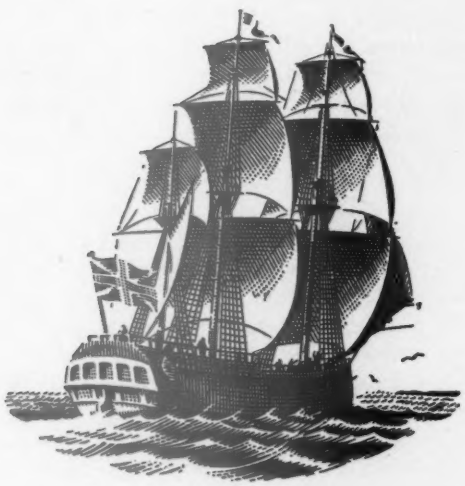
ENDEAVOUR

A quarterly review designed to record the progress of the sciences in the service of mankind



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VOLUME VIII JANUARY 1949 NUMBER 29

The Philosophical Magazine

At the end of the eighteenth century the growing interest and activity in science found expression in what is an outstanding development in the history of exact knowledge, namely the foundation of journals devoted to specialized branches of science. Up to that time the various existing periodicals had dealt with the whole field of scientific endeavour, and sometimes indeed with all learning: now, the needs of those with more limited but more inquiring interests were to be met. In France appeared the *Annales de Chimie*, in Germany the *Journal der Physik* (which later became the *Annalen der Physik und Chemie*), and in England, in 1798, our renowned *Philosophical Magazine*, which has recently marked its 150th anniversary by the issue of a commemoration number devoted mainly to the history of Natural Philosophy in the eighteenth century.

Natural Philosophy was the title chosen by Newton for the book in which he inaugurated a new age in physics and astronomy; Thomas Young in 1807 called his book *Lectures on Natural Philosophy*; and in the Scottish universities physics still goes under the traditional name of natural philosophy. *The Philosophical Magazine* in the beginning reported on matters covering a wide range of interests, including chemistry, astronomy, geology, and occasionally biological subjects, but its interests were largely physical and it gradually acquired fame in civilized countries all over the world as an organ for the speedy publication of results of original research in physics.

The Philosophical Magazine, or 'Phil. Mag.,' as it is briefly—almost affectionately—termed by men of science, has an interesting history. Founded by a Scot, Alexander Tilloch, who for some obscure reason adopted this form in preference to his father's name of Tulloch, it was a private venture, and as such it has developed through its long life to the present day. Since 1827 *The Philosophical Magazine* has been printed by Taylor and Francis at an old house in Red Lion Court, in the City of London, which is a delightful surprise to him who visits it for the first time. The fine seventeenth-century staircase, with the Jacobean twisted wooden columns supporting the balustrade, leads to old rooms in which what are now capacious cupboards were installed as powdering closets in Georgian days. An atmosphere of solid and sober tradition and of good craftsmanship is appropriate for the printing of a scientific journal with its fruit in the present but its roots in the past, for which the careful hand-setting of the much-experienced compositor is necessary if the mathematical machinery of the journal is to show clear.

Looking back to those first days at Red Lion Court, the interest which the world of scientific research came to take in the publication is indicated by the fact that in 1832 David Brewster became one of the editors; he held this position until his death thirty-six years after. Later Kelvin, Lodge, and J. J. Thomson lent as editors the power of their names to promote the influence of the *Magazine*, while the support of Ireland was evidenced by the inclusion of Fitzgerald and John Joly. It is doubtful if these great men took any active part in the running of the paper, especially as they mostly lived at some distance from London, but they were available for consultation, and the presence of their names was a guarantee of the confidence felt by the scientific world in the conduct of the paper. They undoubtedly influenced many first-class workers to contribute to the *Magazine*.

What a list the contributors make! Faraday, Airy, Joule, Rowan Hamilton, Kelvin, Stokes, Rayleigh are British names that come at once to mind, while Helmholtz and Witkowski remind us that the great men of the European mainland

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also sent papers. Some of the greatest American physicists, such as Rowland, published in the *Magazine*; Michelson and Morley's epoch-making paper appeared here in 1887. It was, however, the coming of the electron, of radioactivity, and of other aspects of atomic physics that ushered in the full glory of the 'Phil. Mag.' Not only did J. J. Thomson and Rutherford publish most of their papers there, but so did their collaborators and students, English and foreign. Take down those great books, Thomson's *The Conduction of Electricity Through Gases* and Rutherford's *Radioactivity*, and references to the 'Phil. Mag.' strike the eye at every turn of the page. Rutherford's first paper on the nuclear structure of the atom, Bohr's first papers on atomic structure, Moseley's announcement and development of his law, Aston's early work on isotopes—all appeared in the *Magazine*. It would be an exaggeration, but not a great exaggeration, to say that the whole of the foundations of modern atomic physics could be constructed from the papers contributed to the 'Phil. Mag.' in the thirty years from 1895 onwards.

It would be idle to pretend that *The Philosophical Magazine* enjoys at the moment the glory of the days when it was the main organ of publication of the Cambridge and Manchester schools of research, and when a great question in the laboratories of Europe and America was 'What's in the "Phil. Mag." this month?' Many factors have told against the speedy publication, at one time characteristic, which was possible in former days; the great patrons of the past are gone and their successors have other traditions and other ties; and the proceedings of the learned societies that deal with physics have increased their scope and the efficiency of their machinery for publication. There is, fortunately, little doubt that those responsible for the conduct of the *Magazine* are well apprised of the present position and are taking active steps to ensure that their paper shall resume the important part which it has played in the world of scientific communication. When the *Magazine* first appeared there was no introductory statement on the object or purposes which the editor had in mind: it was left to the reader to gather the policy of the *Magazine* from its content, and no doubt the shaping of this policy was influenced by the course of events. Similarly, at the present time there has been no pronouncement that a process of reform and melioration is in progress, but there are many signs that the proprietors have in hand a vigorous campaign for increasing the usefulness of their paper and for raising the general interest and importance of the communications. We understand that a more rigorous sifting of the contributions submitted has been initiated, and that special efforts are to be made to ensure the prompt appearance of records of really significant researches. Time will show whether papers from special fields are being particularly encouraged, a matter that clearly requires careful consideration by the editorial board. As far as tradition is concerned, at the time of the greatest splendour of the *Magazine* there was a preponderance of papers of a certain type caused by the support of the great schools of research to which reference has been made, but important papers from all branches of physics, both experimental and theoretical, appeared. A definite design will, no doubt, soon show itself. Meanwhile the format of the paper has recently been rendered more attractive, and the editorial board has been strengthened by the addition of Professor N. F. Mott, who—and this is an important step—assumes the duties of active editor. The other members of the editorial board—Sir Lawrence Bragg, Sir George Thomson, and Dr Allan Ferguson (who acted as executive editor for about ten years and did much to raise the standard of the papers)—vouch for the confidence of leaders of research and learning. We look forward with sanguine expectation to the already apparent new period of active renown for the great *Philosophical Magazine* and offer our warmest good wishes for a happy voyage towards the bicentenary.

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Mechanism of chemical reactions

MICHAEL POLANYI

The detailed nature of the mechanism of chemical change was, of course, an insoluble problem until the main principles of atomic structure had been established. During the last two decades, however, much progress has been made, chiefly on the basis of quantum mechanics. Professor Polanyi, himself one of the leading workers in the field, describes the electron-switch theory of chemical reactions and explains some of its applications.

EARLIER DEVELOPMENTS

Twenty years or so ago we already knew that the rate-constants of chemical reactions are of the form given by Arrhenius, $k = Ze^{-Q/RT}$, and the nature of the temperature-independent constant Z was fairly well understood. It meant either the number of collisions occurring per second between reacting molecules (Trautz) or—in the case of unimolecular reactions—the number of fluctuations occurring per second in the energy content of the chemical bond primarily affected by the reaction [1]. It was also clear that the factor $e^{-Q/RT}$ indicated the probability of a collision or a fluctuation overcoming an energy barrier of the height Q. But that was as far as our understanding went. We did not know what the activation energy Q really meant, or what kind of motion the atoms were supposed to be performing in surmounting the energy barrier.

QUANTUM MECHANICS

A new leaf was turned when F. London's paper appeared in 1928 [2]. Here was a principle, set out in terms of the new quantum mechanics, according to which at least the simplest chemical reaction (one free atom attacking a diatomic molecule) could be plausibly represented, and even calculated—though somewhat crudely—in detail. H. Eyring and I took up the idea and worked it out in some concrete examples [3]. It appeared to serve well enough, but the new approach seemed rather abstruse. The further development of this line of thought lay principally in the hands of Eyring and his school, whose work has been summed up in the book by Glasstone, Laidler, and Eyring, *The Theory of Rate Processes* (1941).

THE ELECTRON-SWITCH THEORY OF CHEMICAL REACTIONS

A more direct approach and one which attempts to account for the major variations of chemical reactivity was put forward by Ogg and Polanyi in 1935 [4]. Though it is limited to reactions involving the switch-over of an electron from one centre to another, it covers a wide field of the most common chemical processes. Its principle is this. Consider the spatial arrangement of the elementary particles (atoms or ions) in the initial and final states of a reaction. We shall find in both of these states that atoms coupled by a chemical bond lie closer together than atoms which are not bound together. Since in a chemical reaction there are always bonds broken and new bonds formed, there results a rearrangement of atoms to new partnerships. Atoms which lie close together will become separated, and others formerly wide apart will become close neighbours. Take the simplest case of three particles reacting according to:

$$AX + B = A + XB;$$

it involves moving X from its close association with A and linking it to B instead. Our theory pictures this process as follows. We strain the A-X bond up to a point where X has approached B so closely that it can switch over without any further supply of energy to form the X-B bond. The configuration of the particles at which the electron switch occurs is called the *transition state* of the reaction. The work done in forming the transition state is taken to represent the activation energy Q.

Such a scheme (which must, of course, be elaborated further to be of any practical use) seems directly to suggest some connection between binding strength and chemical reactivity. Suppose we think of the oxidation of a series of hydrocarbons so that A-X represents the C-H bond in the several hydrocarbons, which is to be broken by transfer of H to the oxidizing agent Ox; then we can write the process as

$$R—H + \cdot Ox = R\cdot + HOx$$

where R varies in a series R, R′, R″, . . . , etc. If now we find that some hydrocarbons, e.g.

*iso*butane or toluene, are much more readily oxidized than methane, we may suppose this to be due to less work being required to strain the R-H bonds undergoing oxidation in *iso*butane or toluene than those in methane. In other words we shall try to account for the observed increased reactivities in the series R-H, R′-H, R″-H, etc., by assuming a corresponding fall in the energies of the bonds R-H, R′-H, R″-H, etc.

DETERMINATION OF BOND ENERGIES

In the past ten years it has become increasingly clear that the energy required to split a bond of a particular type, say a C-H, C-OH or C-I bond, does vary to a very marked degree in different organic molecules, and, what is more, we seem to be on our way towards a widely applicable method of determining bond energies in a series of organic compounds.

The method consists in observing the rate of pyrolysis under conditions in which the rate-determining step lies in the rupture of the bond under examination. The first condition is, of course, that this bond must be the weakest in the molecule. For the method to function smoothly, however, it is also necessary that the primary process of bond rupture should be followed neither by a back reaction nor by an indefinitely progressing chain reaction. According to M. Szwarc (1947) [5], this is true for the pyrolysis of toluene. The weakest bond here is a C-H link of the methyl group; and the primary process is accordingly:

$$C_6H_5.CH_3 = C_6H_5.CH_2\cdot + H.$$

Since the H atom immediately reacts with the excess of toluene to produce either H_2 or CH_4 (followed by the formation of dibenzyl and benzene), we have here neither a back reaction nor any consecutive chain reaction, and the number of bonds primarily ruptured per second can be measured by the amount of gas obtained from the pyrolysis.

The observations on the pyrolysis of toluene recorded by Szwarc over a wide range of temperatures do in fact yield a reliable estimate for the bond energy of C-H in the methyl group. The velocity constant obtained is of the form:

$$k = 2 \times 10^{13} \times e^{-\frac{77500}{RT}}$$

The factor 2×10^{13} closely corresponds to the theoretically predicted number of energy fluctuations in the bond broken by pyrolysis, while the quantity 77,500 in the exponent may be taken to represent the energy of that bond in cal/mole.

Similar observations of Szwarc on the pyrolysis of propylene have yielded

$$k = 2{\cdot}5 \times 10^{13} \times e^{-\frac{78000}{RT}}$$

for the rate of dissociation in the methyl group [5*a*].

This reveals a very remarkable drop in the energy of a C-H bond as compared with methane. By a variety of methods (including an indirect application of pyrolysis) it has been established that the dissociation $CH_4 = CH_3 + H$ absorbs 102 kcal/mole. Thus the replacement of an H atom of methane by a phenyl group appears to reduce the C-H bond energy in the methyl group by 24·5 kcal/mole. If such great variations can be brought about in the energies of a carbon-hydrogen bond by the introduction of different substituents on the carbon, then a theory—like the one we suggested—which explains the variable reactivity of such groups by changes of bond energy may seem quite promising. It is important, therefore, to note that a wider application of the method of pyrolysis—to organic iodides, in which as a rule the C-I bond is the weakest—has been attempted with some measure of success, and that this seems to reveal quite marked reductions in bond energy consequent on the lengthening of aliphatic carbon chains and the branching of such chains at the α carbon [6].

Once the variation of energy is determined for one particular carbon link—say for a series of C-I bonds in different positions—the result can be extended by mere calorimetry to other types of carbon bonds having the same positions. Thus the exact calorimetric determination by Rossini [7] of the heats of formation of a series of alcohols R-OH, R′-OH, etc., of the corresponding hydrocarbons R-H, R′-H, etc., yields the variable substitution heats for the sequence of reactions [8]:

$$\text{R-OH} + \text{H} = \text{RH} + \text{OH},$$
$$\text{R′-OH} + \text{H} = \text{R′H} + \text{OH}, \text{ etc.}$$

So if one has obtained the energies of the bonds R-H, R′-H, etc., one can now pass from these to the energies of R-OH, R′-OH, etc.

A. R. Ubbelohde [9] and H. A. Skinner, independently, have recently opened up a line of approach which promises to include in the system of calorimetrically-determined substitution heats the carbon-halogen bonds which are difficult to tackle by combustion calorimetry. Skinner and collaborators [10] determine, for example, the heats of the reactions:

$$Cd(CH_3)_2 + 2H_2O = Cd(OH)_2 + 2CH_4$$
$$\text{and } Cd(CH_3)_2 + 2I_2 = CdI_2 + 2CH_3I,$$

from which they obtain the heat of reaction:

$$CH_3I + H = CH_4 + I.$$

A systematic extension of this method might open up wide fields when combined with further advances in the pyrolytic determination of bond energies.

The results hitherto obtained have already proved that there exist wide variations in the value of these energies. We shall now look into the question of how far the variations may in fact account for the different reactivities of the respective bonds in question.

THE SODIUM FLAME REACTION

I earlier illustrated the electron-switch theory of chemical reactions by reference to a process of oxidation in which a hydrogen atom is transferred to an oxidizing agent which I denoted by Ox. In doing so I had some interesting observations in mind which were brought to my notice in research laboratories at Billingham, showing a striking parallelism between the oxidizability of a series of hydrocarbons by nitrogen dioxide and the reduction in the energies of their weakest C-H bonds as compared with the energy of the C-H bond in methane [11]. The case is of particular interest since oxidation is one of the most important chemical processes, but it has not yet been examined in sufficient detail to serve as material for the application of our theory. Pending such further development—which may soon be brought about by the studies of oxidation now progressing in Leeds under Professor M. G. Evans [12]—we must turn for the illustration of the electron-switch mechanism to the reactions of organic halides with sodium vapour.

It will help to conceive these reactions clearly if we bear in mind the experimental method by which they are observed. The diagram in figure 1 gives an outline of the apparatus. A stream of inert gas at a few millimetres pressure is made to flow through a nozzle, carrying with it a trace of sodium vapour which reacts in front of the nozzle with an excess of the organic halide. The depth is determined to which the sodium vapour penetrates into the space in front of the nozzle before its partial pressure is reduced to a level at which the sodium resonance light becomes imperceptible (that is, about 10^{-5} mm). Other things being equal, the slower the reaction the deeper will be the penetration. The partial pressures of the different organic halides required to maintain the same depth of penetration of the sodium vapour will be the inverse measures of the rates at which these halides react with sodium vapour.

The chemical process involved here may be illustrated for the case of the chlorides. It is:

$$RCl + Na = R\cdot + Cl^- Na^+.$$

The Cl particle is released from its partnership with R and is attached to Na, while R becomes a free radical. This is an electron-switch reaction, for it involves the transfer of an electron from the sodium atom to the chlorine atom. We can see the theoretical treatment outlined in the diagram (figure 2). This illustrates the arrangement of particles in the initial, final, and transition states, and illustrates also the two alternative electronic states of the transition state. We see that in order to make the electron-switch possible it is necessary to elongate the C-Cl bond so as to allow for the increased size of the Cl^- ion formed by transferring an electron from Na to Cl. The energy curves demonstrate the determination of the activation energy on the assumption that the electron-switch occurs at the configuration where the energy is the same before and after the transfer of the electron. The curve on the left (1) represents the energy required to extend the R-X bond and the curve on the right (2) shows the energy of repulsion between the free radical R and the ion X^-. The energy of the transition state is fixed by the crossing of the two, and the activation energy Q is the height of this crossing-point taken from the energy of the initial state [4].

Calculations of the activation energy carried out on this basis have led to values close enough to those observed experimentally [13]. There is a tendency for the predicted values to come out too high, which is due to the fact that the calculation neglects

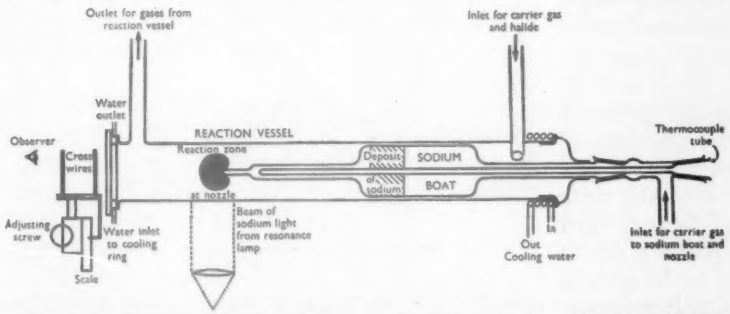

FIGURE 1 – *Diagram of sodium flame apparatus (reaction* $Na + ClR \rightarrow Na^+Cl^- + R$*). The observer adjusts a pair of horizontal wires to the upper and lower edges of the 'reaction zone,' the diameter of which represents the penetration of the sodium vapour into the surrounding halide.*

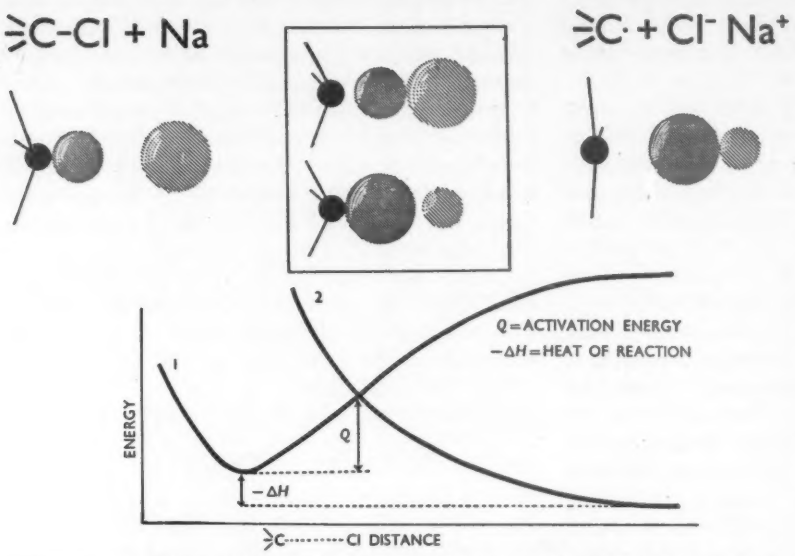

FIGURE 2 – *Theory of the activation energy of the reaction RCl + Na = R· + Cl⁻Na⁺. The 'transition state' shows two resonating configurations, before the electron-switch (above) and after the electron-switch (below). Curve 1 is the bond energy curve of R-Cl. Curve 2 is the repulsion energy curve for the particles R· and Cl⁻.*

the resonance energy possessed by the transition state in view of its two alternative electron configurations. The great simplification achieved by the electron-switch theory as compared with the more rigorous quantum mechanical theory of F. London consists precisely in taking advantage of the fact that this resonance energy can be neglected for a certain type of reaction—though the neglect is sometimes noticeable [14]. This was brought out by M. G. Evans and M. Polanyi in a paper [14] which defined the precise relation of the electron-switch theory to the theory of F. London.

Our energy diagram can be easily expanded to show more precisely how a fall in the energy of the R-X bond may be expected to reduce the activation energy and cause an increase in reactivity. This is shown for a series R-X, R′-X in figure 3. We can also express the relationship which it illustrates as a parallelism between the heats of reaction $-\Delta H$ and the rates of reaction [4, 14]. While the heats of reaction increase by the same amount by which the energies of the ruptured carbon bonds decrease, the corresponding fall in the activation energies Q appear to be only a fraction (a little over a quarter) of this decrease. That is:

$$Q - Q' = \alpha(\Delta H - \Delta H')$$
$$\alpha \sim 0{\cdot}25$$

There is a good deal of evidence to support this conclusion. If we plot the activation energies of the sodium flame reaction (as calculated from the Arrhenius equation $Q = -RT \log k/\mathcal{Z}$) against the approximately known energies of the R-Cl bonds broken in the reaction, we find that a linear relationship of the expected kind fits the data fairly well—at least as long as we limit ourselves to compounds in which R is a pure hydrocarbon radical [6]. When R contains a negative group—for example a CO near the centre of reaction—this causes the reactivity to increase well above the value that would correspond to the bond energy R-Cl. The reason seems to lie in an increase of the resonance energy in the transition state, originating in the presence of additional electronic configurations [15]. This effect is well illustrated by recent observations of E. Warhurst and his collaborators on the sodium flame reactions of the ortho-, meta-, and para-methoxy-bromobenzenes [16]. The ortho- compound reacted three times as fast, the meta- compound 1·5 times as fast, and the para- compound at the same rate, as bromobenzene. Besides the two electronic

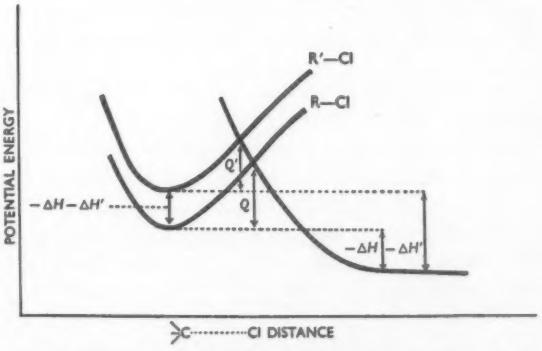

FIGURE 3 – *Illustration of the relationship* $Q - Q' = \alpha(\Delta H - \Delta H')$, *where* $\alpha < 0{\cdot}5$. *The diagram applies the derivation of the activation energy (shown in figure 2) to the case of two compounds RCl and R′Cl, the bond energies of which differ by the amount* $\Delta H - \Delta H'$.

configurations corresponding to the initial and final states, the transition state contains here the additional configuration of the type:

$$CH_3O^- \cdot C_6H_4Br \quad Na^+,$$

the stability of which—and their consequent effectiveness in lowering the energy of the transition state—depends on the proximity of the two oppositely charged centres, which is greater for ortho- than for meta-, and again for meta- than for para- methoxy-bromobenzene. This accounts for the observed sequence of the reactivities of these compounds.

Before leaving the reaction between sodium vapour and the organic halides I should like to point out why it holds a peculiar and—as it would seem to me—a theoretically important position among organic reactions. It is a bimolecular gas reaction, and as such it represents the collision between two particles only. (Reactions in solution are in general complicated by the part played by the solvent.) Moreover, the theoretical treatment of the variable reactivities of the different organic radicals R, R′, etc., is greatly simplified by the fact that only three atoms have to be considered in the process: the α-carbon C, the halogen X attached to C, and the Na atom attacking X. Whatever substituents we attach to the C atom, they will affect the reaction only by modifying the C-X bond, for they are well out of the way of the attacking Na atom and do not interfere with its approach to the X atom. In other words, we can exclude in this case any steric hindrance on the part of substituents attached to the α-carbon. It also greatly simplifies the theory that the organic radical forms part of only the bond that is broken and not of the bond that is formed in the reaction. Only where this is true can the relationship hold that $Q - Q' = \alpha(\triangle H - \triangle H')$.

It is difficult to see how any other reaction could be found that is theoretically quite as simple as the sodium flame reaction.

SUBSTITUTION BY NEGATIVE IONS

The distinctive characteristics of the sodium flame reaction may become clearer by contrast if we now turn to another comparatively simple series of reactions—the more so since this series again involves the same series of organic halides. I am referring to the ionic substitution commonly exemplified by:

$$I^- + RCl = IR + Cl^-,$$

and usually carried out in solution in acetone. We may start off once more by picturing the initial and final arrangements of the reacting particles and constructing the transition state which leads from one to the other. Disregarding the molecules of the solvent, which is often permissible in this case, we may take figure 4 to represent the initial and final stages and the transition state for the case of an ionic exchange reaction:

$$I^- + RI = IR + I^-.$$

We notice that the reaction involves an optical inversion at the α-carbon (Meer and Polanyi, 1931) [17]. This was first confirmed by the study of racemization of optically active halides under the influence of the halogen ion [18]. The kinetics of this process were shown to reflect an underlying ionic exchange reaction, as represented for example by:

$$I^- + l\text{-}RI = d\text{-}IR + I^-,$$

which leads to an equilibrium mixture of the two optical antipodes. A final confirmation of the theory was given by Hughes and collaborators [19] by the use of radioactive tracers, which enabled them to determine directly the rate of the atomic exchange reaction and compare it with the rate of the accompanying process of racemization.

I have attached no energy diagram to figure 4, since in this case the energy function is too complex to be represented by a chart. We can, however, readily recognize the elements which make up the energy of the transition state. In either of the two electronic states there are present both the strain due to extension of a carbon-halogen bond and the pressure exercised by a halogen ion on the carbon centre. Some pressure will also be exercised on the substituents attached to the carbon centre, and we can foresee that if these are voluminous they might very effectively shield the

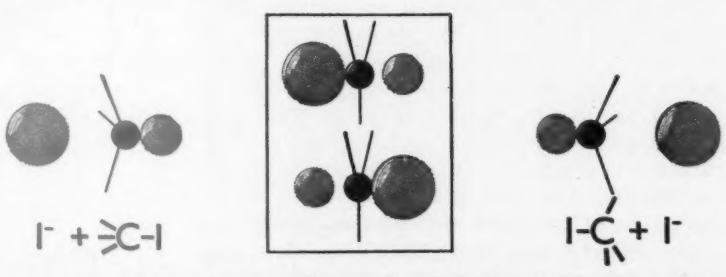

FIGURE 4 – *Configuration in the initial state and final state of the ionic exchange reaction* $I^- + RI = IR + I^-$. *The transition state between the two shows the configuration before the electron-switch (above) and after the electron-switch (below).*

centre from attack by an ion seeking to enter into reaction with it. Hence this type of reaction should show considerable steric hindrance by substituents attached to the α-carbon.

These factors were recognized from the start, in a general way, when the electron-switch theory of reactions was first put forward; the decisive importance of steric hindrance for reactions of the type under consideration had indeed been postulated already by Meer and Polanyi in 1931, who explained the decrease in the rate of ionic substitution in the series of the C_2H_5-, sec. C_3H_7-, tert. C_4H_9- halides by the increasing steric hindrance caused by the successive replacement of hydrogen atoms by the more voluminous methyl groups.

The theory outlined above was also used for detailed calculations of activation energies based on this theory, which were first made for atomic exchange reactions of the type $I^- + CH_3I = ICH_3 + I^-$, where steric hindrance could be disregarded [4]. The results agreed well enough with experience, though the calculated figures again tended to be somewhat in excess of those observed, which might be due to the fact that the electron-switch theory neglects the resonance energy in the transition state.

A more extensive theoretical attack on reactions of this type had to wait until methods were found of calculating the effects of steric hindrance on reaction rates. This was achieved, broadly speaking, by taking into account the van der Waals radius of substituents [20]. We may illustrate this by a picture (figure 5) showing how the methyl groups attached to the α-carbon in *tert.*-butyl chloride obstruct the approach of a Cl^- ion to the reaction centre. These groups are represented here in the way they appear in the well-known Fisher models, the atoms being enlarged on their outer side by 0·6–0·8 A as compared with their atomic radius derived from bond distances.

A recent application of these principles in detail to the known observed material has been made by A. G. Evans [21]. It is now clear that when one replaces a hydrogen atom in a methyl halide one introduces as a rule a steric hindrance to ionic substitution which greatly outweighs in its effect that of any concomitant weakening of the carbon-halogen bond, which by itself would facilitate the reaction. This is always true for the replacement of hydrogen atoms by methyl groups at the carbon centre. There are, however, at least two cases in which it does not hold. Substitution by the phenyl and the vinyl radicals can be shown to cause no marked steric hindrance, while its weakening effect on the energy of the carbon-halogen bond is known to be very large. In these cases, therefore—that is for the benzyl- and allyl-halides—ionic substitution should be much faster than for the ethyl compound, and this is confirmed by experience. The theory permits the assessment of all these effects in a semi-quantitative manner and the results are found to agree sufficiently with experience.

When we come to radicals which contain negative groups we meet a similar acceleration, due to additional resonance in the transition state, as we have seen in the case of the sodium flame reaction; the electron of the attacking ion plays here the part of the electron of the sodium atom [15]. These effects require further elucidation.

Meanwhile we may conclude that the ionic substitution of organic halides introduces one important additional factor to those which determine the rate of the sodium flame reaction, namely the steric hindrance caused by voluminous substituents on the α-carbon. The effect of this outweighs as a rule—though not invariably—the effects of changing bond energies, which dominate the sequence of reactivities in the sodium flame.

UNIMOLECULAR SOLVOLYSIS

There exists yet another type of reaction which is well suited for a systematic examination of reactivity in a series of organic compounds, and which can also be satisfactorily analysed in terms of the electron-switch mechanism of chemical reactions. It is the unimolecular solvolysis of organic halides, which was proved by Ingold and

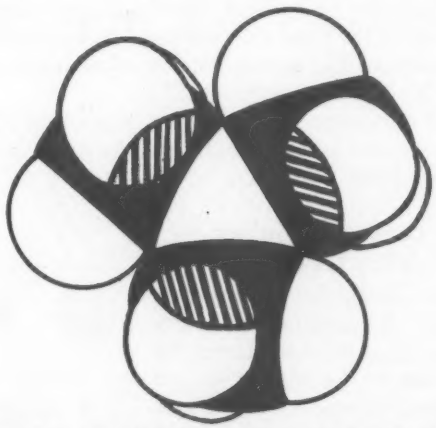

FIGURE 5 – *Model of the transition of* tert.*-butyl chloride for the reaction* $Cl^- + (CH_3)_3C.Cl = Cl.C(CH_3)_3 + Cl^-$. *The hydrogen atoms are shaded to show the penetration of the Cl particles.*

his school to be initiated and governed in its progress by an electrolytic dissociation into a positive carbonium and a negative halogen ion, $RX = R^+ + X^-$, following which the carbonium ion reacts with the solvent and forms the stable products of the solvolysis.

It is not possible in this case to draw a complete diagram of the atomic arrangement in the initial and final states, for the production of a pair of ions from a neutral pair of atoms necessarily involves a far-reaching reorganization of the solvent molecules, and we can picture only the ions, not their solvation shells. Figure 6 (top) indicates the configuration of the central particles—the α-carbon and the halogen—in the initial and final states of the primary process of unimolecular solvolysis.

We notice once more that the reaction involves an extension of the C-X bond to allow for the enlargement of the X atom when it changes into an X^- ion. The extension is somewhat lessened by the accompanying reduction of the C atom, which undergoes the loss of an electron. Much more important, however—in comparing this reaction with the two that we studied before—is the fact that the ionization at the carbon centre introduces two new magnitudes, namely the ionization energy (I) of the radical and the solvation energy (S^+) of the resultant carbonium ion.

The energy chart of this reaction can be readily outlined (see figure 6 [bottom]). The initial state is represented once more by the curve showing the energy change for the extension of the C-X bond. For the final state we have a new curve representing the energy of the two ions R^+ and Cl^- in a solvent. Where the two curves cross, the electron-switch can take place without change of energy, which according to our theory is the characteristic of the transition state, and the energy Q of the transition state—measured from the initial state—gives us the activation energy of the reaction. The diagram shows that Q does not differ appreciably from the energy of the electrolytic dissociation ED, which is also marked in the figure [23]. We shall accordingly take the magnitude of the latter to represent the value of Q.

This manner of estimating the activation energy of a unimolecular solvolysis leads quite easily to the following expression:

$$Q = D + I - E - S^- - S^+,$$

where D is the energy of the C-X bond, I the ionization potential of the radical R, E the electron affinity of the halogen X, S^- the solvation energy of the halogen ion X^-, and S^+ the solvation energy

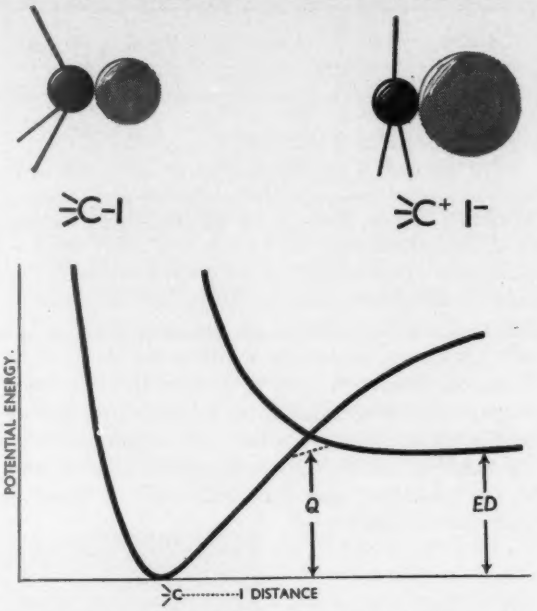

FIGURE 6 – *Illustration of the electronic reaction* $RI = R^+ + I^-$.

of the carbonium ion R^+. If we consider a series of compounds R-X, R′-X, etc., containing the same halogen atom, the variation of Q will be determined by the changes of the magnitude $D + I - S^+$.

This theory was first outlined when the electron-switch theory was originally established [4]. With the assumption, however, that the ionization potential of radicals is constant [23], which seemed justifiable at the time, it encountered great difficulties when applied to experience. It appeared, in particular, to give no explanation for the striking increase in the rate of solvolysis —to more than a millionfold—observed by Ingold in the series ethyl, *iso*propyl, *tert.*-butyl. The answer to this problem was only recently discovered by A. G. Evans [21] in the fact—which he drew from observations of American physicists [24]—that the ionization potential I of organic radicals varies over a much wider range of values than we had ever thought possible before. A. G. Evans has summarized the position in the table on page 10, which refers to the alkyl iodides with water as solvent.

UNIMOLECULAR HYDROLYSIS OF ALKYL IODIDES

In the last column is shown the predicted fall in the value of the activation energy (at absolute zero), which amounts to 63 kcal over the range of the

Radical	*D*	*I*	S^+	$(D + I - S^+)$	ΔQ
CH_3 ..	54·0	232	82	204	30
CH_3CH_2 ..	52·0	200	78	174	22
$CH(CH_3)_2$	46·5	179	74	152	11
$C(CH_3)_3$ ..	45·0	165	69	141	

whole series. In spite of the approximate nature of these calculations it is clear that they offer a satisfactory explanation of the great increase in the rate of solvolysis which accompanies the attachment of methyl groups to the α-carbon. This effect appears as due to a fall in the ionization potential from 232 to 165 kcal/mole. We may note the opposing effect of the fall in S^+, the solvation energy of the carbonium ion, which is due to the shielding effect of the voluminous substituents at the α-carbon and thus represents a kind of steric hindrance.

GENERAL CONCLUSIONS

The activation energies of the three reactions which we have surveyed in turn thus appear to be determined by an increasing number of parameters. For the sodium flame reactions Q depended (in simple cases) mainly on the energy of the R-X bond. For the ionic substitution reaction we had to add steric hindrance as a second powerful factor. And lastly, for the unimolecular solvolysis, we have to consider also changes in the ionization potential of the radical R.

Thus even for our selected group of simplest reactions we seem to be facing many complications, but this much I think may be claimed nevertheless: that the broad principles governing the mechanism of chemical reactions have become clearly visible, and that it seems possible to account in an approximate manner for the observed rate of a number of different reactions.

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[12] Based on public lectures of Professor M. G. EVANS, the substance of which I understand is in the course of publication.

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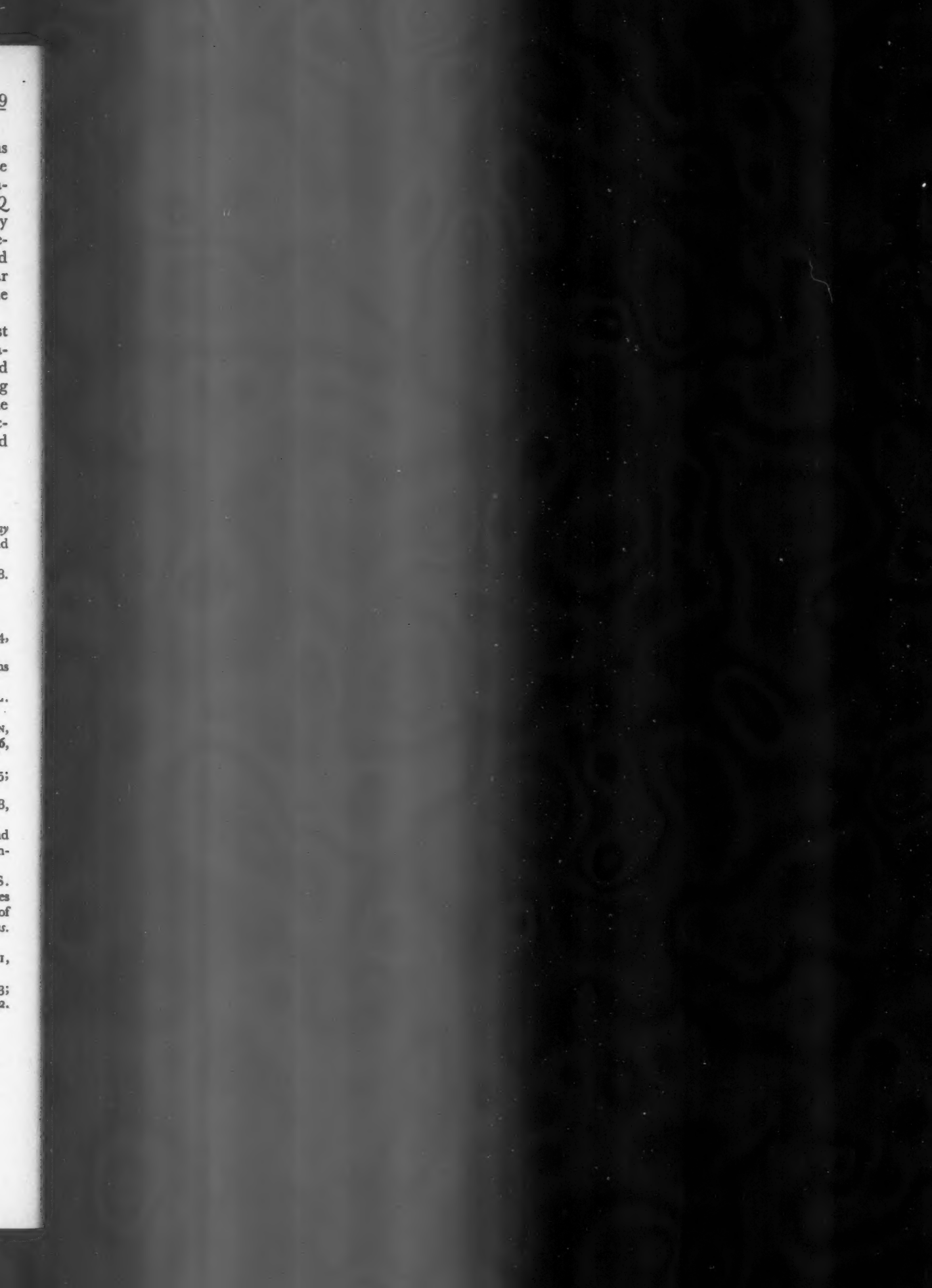

Captain James Cook, R.N., F.R.S.

SIR MAURICE HOLMES

Captain James Cook, after whose celebrated bark *Endeavour* this journal is named, charted much of the Pacific Ocean, Australia, and New Zealand, and originated scientific marine surveying. Sir Maurice Holmes here describes the main events of the great navigator's life. The painting of the *Endeavour* by Commander R. Langmaid, R.N. (retd.), from which the plate on page 14 is reproduced, is based on a contemporary drawing and on all available authentic data, and is probably the most accurate representation of the bark ever made.

James Cook furnishes a notable example of the fact that a sound constitution, a stout heart, and steady nerves are ample compensation for the accident of lowly birth. His father was an agricultural labourer, employed at the time of James's birth—27th October, 1728—at Marton, near Middlesbrough. Here James learned his letters, and on his father's transference as bailiff to a farm near Great Ayton attended the local school, where he mastered the three R's. In 1745 he went as shop-boy in a grocer's shop at the seaside village of Staithes, kept by a Mr Saunderson. Here he was drawn by the lure of the sea and was apprenticed to a Mr Walker, coal-shipper of Whitby. His experience gained during the next eight years, together with the study of Euclid and elementary navigation in his master's house when his ship was not at sea, was to prove of great value in later years.

FIGURE 1 – *Engraving of James Cook by Sherwin, after a painting by N. Dance. David Sambwell* (Narrative of the Death of Captain James Cook, 1786) *says that this is an excellent likeness and, indeed, the only portrait which bears any resemblance to him.*

In 1755 Cook was offered the command of Mr Walker's latest ship, but declined it and volunteered into the Royal Navy as an able-bodied seaman, having, as he afterwards said, 'a mind to try my fortune that way.' His first ship was the *Eagle*, and, soon after he joined, the command was given to Captain (later Sir Hugh) Palliser, who was destined to have a great influence on Cook's career and to become his close friend. Cook's service in the *Eagle* coincided with the opening years of the Seven Years' War. After two years, during which he saw a certain amount of action, Cook was promoted to the *Pembroke* as Master, and sailed for Louisburg for the attack on French Canada. This gave him the opportunity for his first hydrographical experiment, the surveying of the St. Lawrence, a task so brilliantly accomplished that he received a special grant of £50. This led, after Cook's return to England, to further work of a similar kind.

Thus we find him in 1763 engaged on the coastal survey of Newfoundland, and here he was joined in the following year by Palliser, who was appointed Governor of the island. For the next four years his life followed the same pattern, the winter being spent in England and the rest of the year in Newfoundland. But during this period there was one incident which had a profound effect on Cook's future career. In 1766 an observation by him of an eclipse of the sun taken near Cape Ray was communicated to the Royal Society and published in their *Transactions*. Two years later the fruits of that incident and of Cook's long apprenticeship as a marine surveyor became apparent. In 1768 he set out on his first voyage round the world.

FIGURE 2 – Resolution *and* Discovery *in Queen Charlotte Sound, New Zealand. From an aquatint by Piringer after J. Clevely.*

FIGURE 2 – Resolution *and* Discovery *in Queen Charlotte Sound, New Zealand. From an aquatint by Piringer after J. Clevely.*

FIGURE 3 – *The death of Cook, from a picture on glass after the painting by G. Carter.*

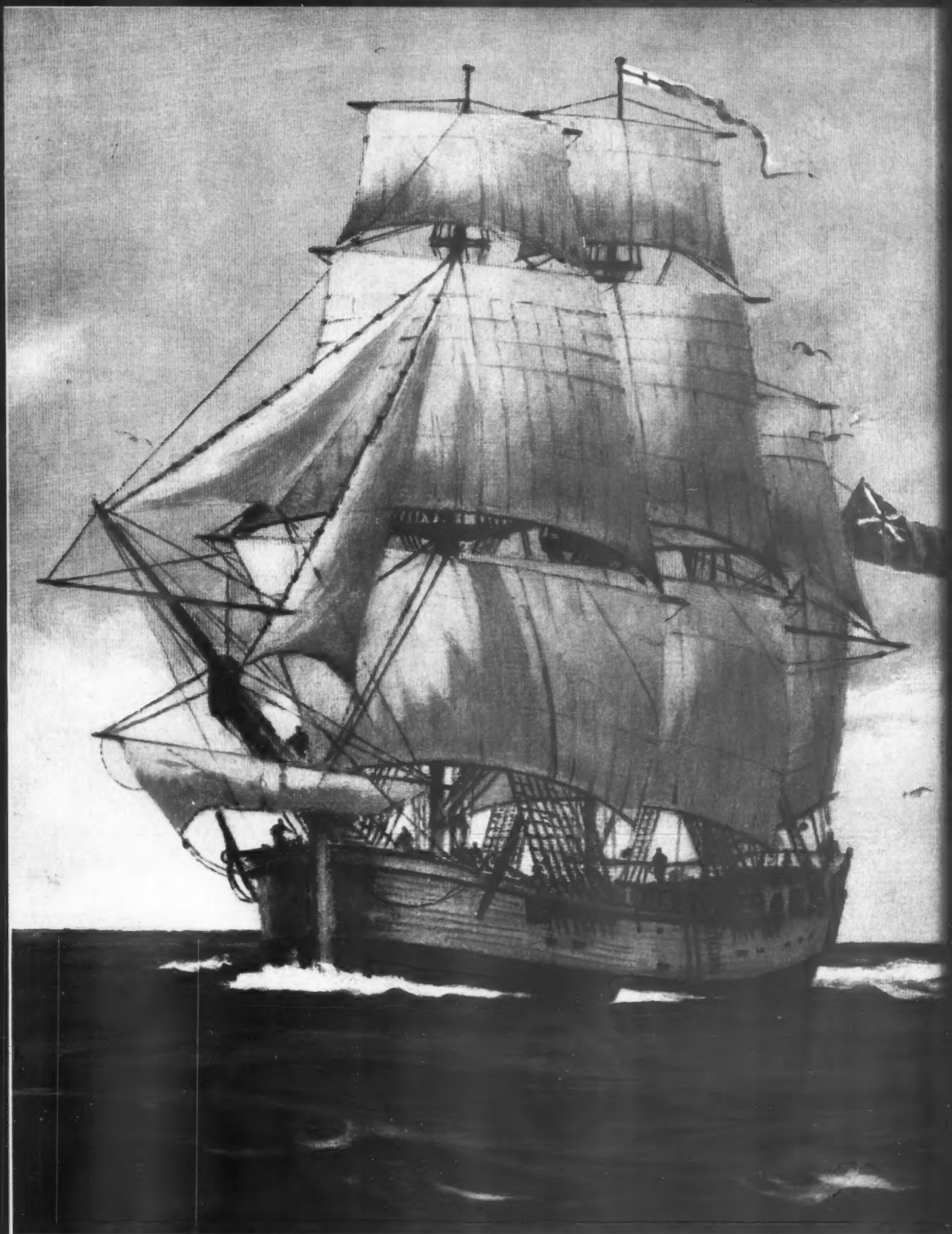

FIGURE 4 – Endeavour. *From an imaginative study made for this article by R. Langmaid and based upon all available authentic data.*

FIRST VOYAGE, 1768–71

The motives which underlay Cook's first circumnavigation were partly scientific, partly geographical, and partly imperialistic. It was known that in 1769 there would be a transit of Venus, accurate observation of which would determine the earth's distance from the sun, and that a similar opportunity would not recur for over a century. The Royal Society accordingly petitioned the King for a grant-in-aid of £4,000 towards the expense of sending out an expedition to an appropriate spot from which the necessary observation could be made. This proposal accorded well with the views of the Government, who were anxious to dispose once and for all of the theory, dear to the hearts of many armchair geographers, that there must be an unknown Southern Continent to counterbalance the known mass of land north of the Equator, and who were even more anxious to secure that, if there were new lands to discover and annex, they should fall to Great Britain and not to France.

The Royal Society's memorial was accordingly well received and the necessary financial provision was granted. The next question was who should command the expedition. The essential qualifications were that the commander should be a naval officer, that he should be an expert marine surveyor, and that he should have some knowledge of astronomy. Cook alone completely filled the bill, and on 25th May, 1768, through Palliser's recommendation, he was given command of the expedition with the rank of First Lieutenant. The choice of a ship was left largely to him, and, realizing the need for a ship which could take the ground and be laid on shore for repair, he chose a type with which he was very familiar, viz. a Whitby collier—a ship which was to achieve immortality as the *Endeavour*.

Cook's instructions, in a nutshell, were to observe the transit at Tahiti, then to sail south to the latitude of 40° and search for the Southern Continent between that latitude and 35° until he found it or fell in with New Zealand, a tiny portion of the South Island of which had been charted by Tasman. If the Continent were not discovered he was to explore the coast of New Zealand and return home via the Cape or Cape Horn. With the consent of the natives he was to take possession of unexplored countries in the King's name.

On 25th August, 1768, Cook set sail, accompanied, among others, by Green the astronomer and young Joseph Banks, who was in later life to be president of the Royal Society for many years. The transit was duly observed by Cook and Green independently, and, after discovering and charting the Society Islands to the westward, Cook sailed south. Finding no signs of a continent he made for New Zealand, which, in the opinion of some theorists, constituted a tip of the Continent. This theory was exploded by a complete circumnavigation of both islands.

Cook was now due to sail home either by the Cape or Cape Horn, but, acting on a discretion which his instructions permitted, he decided to steer westward until he fell in with the hitherto unexplored east coast of Australia and follow it northward. Had he foreseen the appalling perils of that journey, sometimes inside and sometimes outside the Great Barrier Reef, and his providential escape from shipwreck when the *Endeavour* grounded, he might well have chosen otherwise. As it was, after landing at Botany Bay he pursued his course northward, took possession of the east coast of Australia, confirmed the doubtful point of the separation of Australia from New Guinea, and reached Batavia. Here malaria and dysentery took their toll, and the *Endeavour* reached England with a sadly reduced company.

Cook had done all, and more than all, that he had been told to do. He had observed the transit, charted New Zealand, and demonstrated that the Southern Continent, if it existed at all, was much less extensive than its protagonists claimed. In addition, he had charted the east coast of Australia and confirmed the existence of Torres Strait.

SECOND VOYAGE, 1772–5

Although, as has been shown, Cook had administered a severe shock to the continent-mongers, he had not wholly disposed of their thesis. They contended that land in the South Atlantic which Bouvet de Lozier had sighted in foggy weather in 1739 might well be part of the Continent. This land was placed by Bouvet in lat. 54° 00′S, long. 11° 20′E. and named Cape Circumcision. Cook's instructions were to proceed by way of the Cape to Cape Circumcision and ascertain whether it was part of the Continent, and, if it was, to explore it and take possession of it. If it proved to be an island, or if he could not find it, he was to go as far south as possible and, turning eastward, circumnavigate the globe in the highest possible southern latitude.

Remembering the hazards of his first voyage, Cook would not trust himself to a single ship, and

chose two Whitby ships, the *Resolution* and the *Adventure* (Captain Furneaux). Two naturalists, father and son, named Forster, and two astronomers, Wales and Bayly, accompanied the expedition.

The ships set sail on 13th July, 1772, and after leaving the Cape on 22nd November Cook began a long and laborious search for Cape Circumcision. Having concluded that, whether it existed or not, it could not be part of a continent, Cook turned eastward and began his circumnavigation. On 17th January, 1773, he made the first crossing in history of the Antarctic Circle, and continued eastwards until he had covered more than a third of the earth's circumference. The dangers from ice and fog were almost perpetual, and it is not surprising that the ships parted company, at first temporarily and ultimately for good. After Cook had been driven northward to Queen Charlotte Sound by the season of the year and the need for a refit, he set out to complete his task, and, as an examination of the chart of this voyage will show, succeeded in doing what he had been told to do by sailing round the world in the highest possible southern latitude. It is true that he did not discover Cape Circumcision, but that was because Bouvet had seriously misplaced it in his chart. Now known as Bouvet Island, it lies in lat. 54° 26′S, long. 3° 24′E. He discovered no Southern Continent because such a continent, with its reputed 50 million inhabitants and great riches, does not exist—though had he been able to sail a hundred miles still farther south he would have found the unpeopled desert of Antarctica.

The failure to find the Southern Continent was compensated for in Cook's mind by his complete conquest of scurvy, a feat which, he wrote, 'will make this Voyage remarkable in the opinion of every benevolent person, when the disputes about a Southern Continent shall have ceased to engage the attention, and to divide the judgment of philosophers.' In his paper on the subject, which earned him the Copley medal of the Royal Society, Cook described his methods. Briefly, they consisted of insistence on the regular use of anti-scorbutics and the cleanliness of his men's bodies and clothing, the ventilation of his ships, taking on fresh water wherever possible, and keeping the men fully employed.

Soon after his return Cook was promoted post-captain and given a sinecure as one of the captains of Greenwich Hospital, with an official residence and £200 a year. However, a leisured and dignified retirement was not to be his lot.

THIRD VOYAGE, 1776–80

Having finally disposed of one age-long theory, the Great Southern Continent, the Admiralty was anxious to dispose of another which had long exercised the minds of geographers and explorers, namely the existence of a northern sea-passage connecting the Pacific with the Atlantic. Such a route, if it existed, would be very much shorter than the alternative one round Cape Horn or through the Straits of Magellan. The Admiralty felt it hardly fair to invite Cook to command the expedition, but on hearing of the project he immediately volunteered to do so. The ships were again Whitby-built: the *Resolution* in which he had sailed in the previous voyage, and the *Discovery* (Captain Clerke).

Cook's instructions, in brief, were to sail via the Cape to Tahiti, and after repatriating, either there or at the Society Islands, a native called Omai whom Furneaux had brought home with him on the second voyage, to make for the west coast of America in about 45° N and then press on to 65°, where he was to begin his search for a passage running towards Hudson Bay or Baffin Bay. If unsuccessful he was to winter in Kamchatka, and in the next year to try again farther north for a north-west passage to the Atlantic, or failing this, a north-east passage round Siberia and northern Russia.

The *Resolution* sailed on 12th July, 1776, and the *Discovery* on 1st August. On arrival at Tahiti Cook decided that Omai would be happier in one of the Society Islands and deposited him at Huahine. He then pressed northward, and on 18th January, 1778, sighted the first of a group of islands which he named the Sandwich Islands. In March he anchored in Nootka Sound without realizing the insularity of Vancouver. Keeping a close watch as he sailed northward for any opening in the coastline that might develop into a channel, he tried the only one he found (Cook Inlet) without success, and the ships made for Bering Strait, where they anchored in August.

Owing to the lateness of the season, further search for the passage had to be deferred, and Cook decided to make for the Sandwich Islands. On 30th November he sighted a new island, Hawaii, by far the largest of the group. After charting it he anchored in Kealakekua Bay. Here, owing to the supposition of the natives that he was a reincarnation of one of their gods, he was treated with adoration, and all possible supplies were forthcoming. In February, 1779, Cook left the island to resume his task. A few days later the

Resolution sprung her top-mast, and Cook decided to return to Kealakekua Bay. The natives, who had been almost eaten out of hearth and home, were less friendly, and on the night of 13th February the *Discovery's* cutter was stolen. Cook decided on a stratagem which he had often adopted in cases of theft: he would induce the king to come aboard and hold him hostage until the cutter was restored. The king made no demur, but his people did their best to dissuade him. While he was hesitating, news came that a chief had been killed while trying to escape from the bay in a canoe. Pandemonium followed and the natives set upon the escort of marines. Cook they did not dare to attack while he faced them, but when he turned to call upon the boats to cease fire he was fatally stabbed in the back.

This last voyage failed of its purpose—a failure to achieve the impossible—but, by way of compensation, the North Pacific and the Sandwich Islands found their places on the map.

Cook's contributions to the sum of human knowledge were so striking, and the fields which they covered so wide, that any attempt to summarize them must be inadequate. On the geographical side he drew back the curtain which shrouded the Pacific and disposed, once and for all, of the supposed Great Southern Continent, giving us in its place the east coastline of Australia, the map of New Zealand in all essentials as we know it today, the first vision of the Antarctic Circle, and the Sandwich Islands.

Despite his inadequate schooling he acquired, through private study in his leisure time, a considerable knowledge of mathematics, astronomy, and other branches of science, and he had a natural skill in draughtsmanship. He possessed the true scientific outlook; to be of service to geography, navigation, and other sciences was always his aim. Although astronomers were appointed to accompany his expeditions, Cook himself took the lead in the various observations of an astronomical kind made in the course of his voyages. His early observation of the eclipse of the sun in 1766 was used for the practical purpose of fixing the longitude of the place of observation.

The latitudes and longitudes of the places he visited were carefully determined by astronomical observations. On the second and third voyages he had with him the Larcum Kendall copy of Harrison's timepiece No. 4, and in several places in his journal he wrote with high appreciation of 'our never failing guide, the watch.' His positions were of a higher accuracy than had been attained by earlier navigators. Many gross errors in the positions of various places were found, and great improvements were made in the maps of the regions he visited.

Cook was, as various hydrographers to the Royal Navy have testified, the originator of scientific marine surveying. Coastlines were accurately delineated, numerous soundings were made, and the correct draughts of channels were determined. His charts were unsurpassed in his time for their accuracy and excellence. Many determinations of the variation of the compass were made, and the nature of the tides in various regions was studied and recorded. On his voyages to the far south, the Aurora Australis was observed. His conquest of scurvy and the proof that this scourge, with its appalling death-roll, was not a necessary concomitant of prolonged sea voyages, was not the least of his achievements. He was elected a Fellow of the Royal Society in 1776.

The secret of Cook's success lay in his complete singleness of purpose and his infinite capacity for taking pains. In the words of the motto embodied in his coat of arms, *Nil intentatum reliquit.* These are not spectacular attributes, but they were precisely those needed for his tasks, and they accord well with the names of his ships—*Endeavour*, *Resolution*, *Adventure*, and *Discovery*.

Leaf shape and physiological age

ERIC ASHBY

Professor Ashby observes that the change in shape from leaf to leaf on a stem raises four major problems: how shape is determined by local differences in cell division and growth; the chemical and physical background to these differences; the mechanisms by which environment affects leaf shape; and whether leaf shape is related to maturity. In the present article the last two of these problems are discussed and illustrated. Modern techniques show promise of ultimately revealing the basic causes and significance of leaf shape.

Ever since Theophrastus described the variation in shape of ivy leaves[1] there have been records of observations and speculations on leaf shape. Ruskin marvelled at its variety, 'never the same from footstalk to blossom.' Lord Avebury felt it necessary to warn his readers against 'the widely prevalent idea that the variety of leaves is a beneficent arrangement made specially with reference to the enjoyment and delight of man.' Botanists at the close of the nineteenth century believed that the ontogeny of leaf shape in individuals recapitulated the phylogeny of leaf shape in the taxonomic groups to which the individuals belonged. At the turn of the century all these comprehensive generalizations had evaporated, and modern botanists have inherited a mass of observations about leaf shape, not co-ordinated by any satisfactory hypothesis.

Recently there has been a notable revival of interest in the problems of plant morphology. The determination of shape and pattern in plants is now being studied with the techniques of genetics and physiology. One aspect of this revival, namely the study of morphogenesis at the meristems of ferns, has already been discussed in this journal.[2] The present article describes another aspect, namely the modern approach to the analysis of leaf shape in flowering plants.

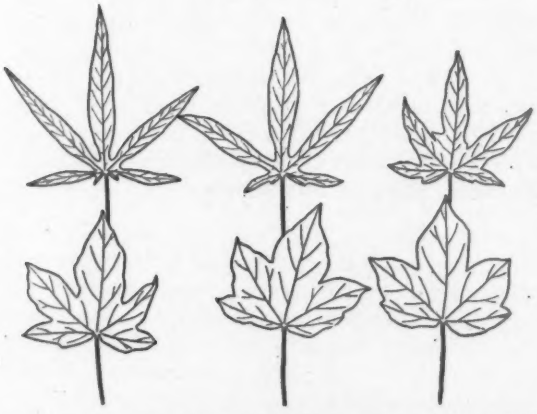

FIGURE 1 – *Leaves of six different strains of the Asiatic cotton* Gossypium arboreum. *Each shape is controlled by a specific gene.* (*From D. Hammond,* American Journal of Botany, *by permission of the publishers.*)

It is common knowledge that the shapes of leaves vary not only between varieties, but also on one and the same plant. Differences in leaf shape between varieties are due to gene differences. In the Asiatic cotton, *Gossypium arboreum*, for instance, there are at least six alternative leaf shapes (figure 1), each controlled by a specific gene. To say that leaf shape is controlled by genes does not, of course, contribute much to its analysis; the mechanism of gene action is not understood, and the problem of how genes act on leaf shape cannot be solved without solving the problem of gene action in general. In the initial stages of the analysis of leaf shape it is desirable, therefore, to exclude genetic variations, and to study only the variation of leaf shape on one and the same plant.

Observation of the shoots of flowering plants reveals the fact that successive leaves on a stem are not alike. Although all leaves begin as 'mounds' of dividing cells (figure 6), yet each adult leaf differs in shape from the leaf below it. The differences are not haphazard: they follow a consistent trend from node to node. The trend may be an increase in the amount of segmentation (as in the delphinium, figure 8*a*) or an increase in the amount of lobing (as in morning glory, figure 8*b*), or it may be a change in the relative lengths of leaf blade and petiole, together with a change in the angle between the leaf base and the petiole (as in sugar beet, figure 8*c*). These trends can be expressed quantitatively by plotting an appropriate measure of leaf shape against the

[1] *Inquiry into Plants*, i, x.

[2] ENDEAVOUR, v, 17, 1946.

FIGURE 2 – *Common harebell.*
(a) *Normal plant with juvenile and adult foliage.*
(b) *Plant grown in shade.*
(c) *Plant from cutting.*
(*From a drawing by E. H. Roberts.*)

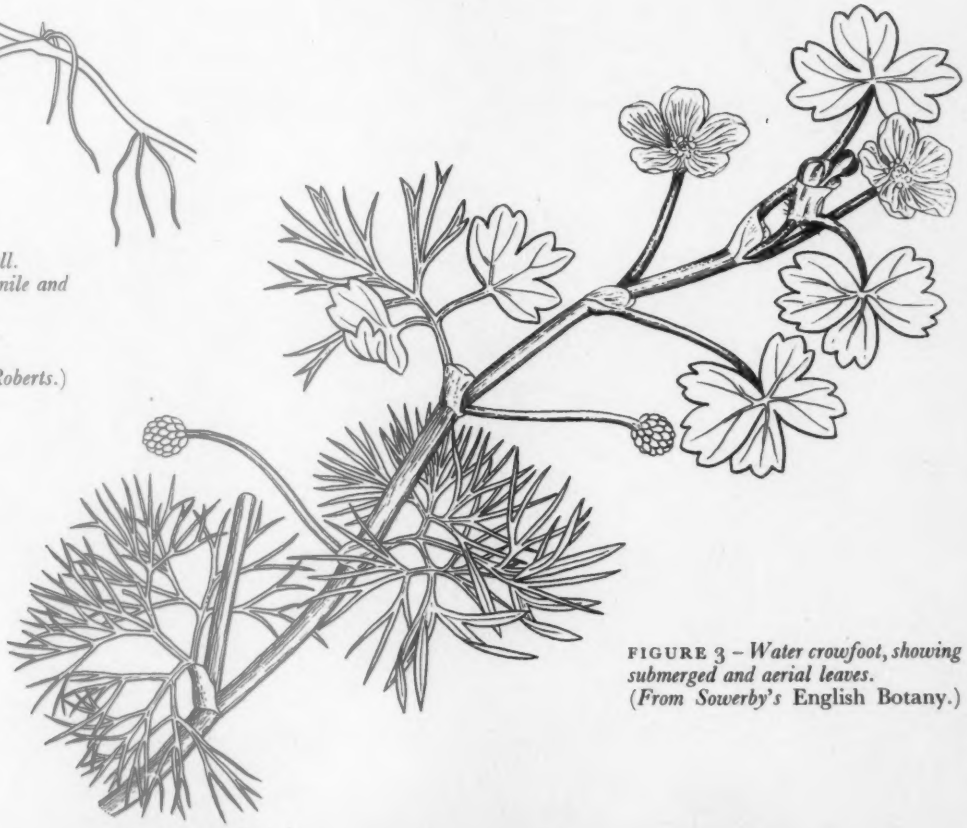

FIGURE 3 – *Water crowfoot, showing submerged and aerial leaves.*
(*From Sowerby's* English Botany.)

FIGURE 4 – Eucalyptus Macarthuri, *showing juvenile leaves (left) and adult leaves (right).* (*From Baker and Smith,* A Research on the Eucalypts and their Essential Oils.)

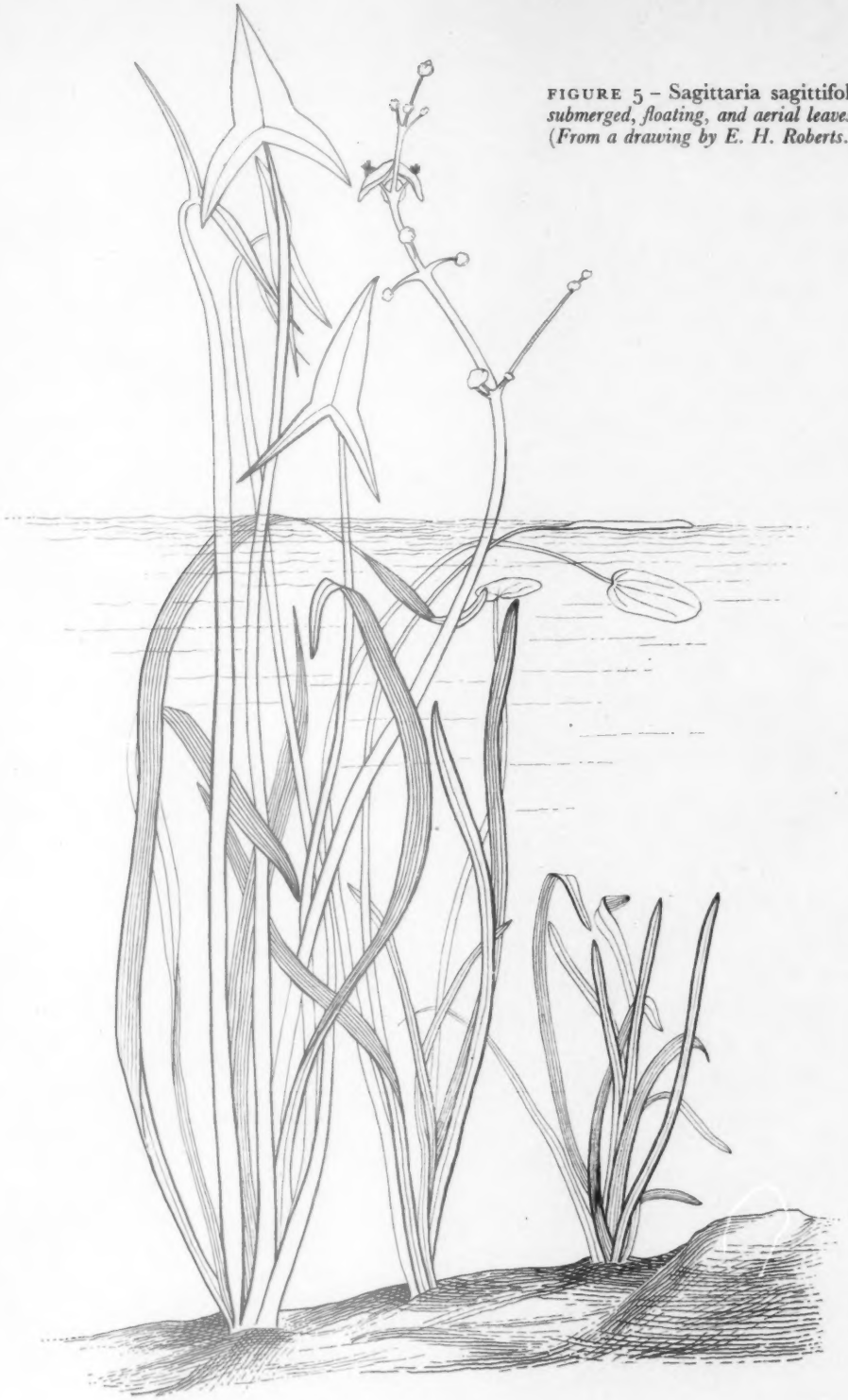

FIGURE 5 – Sagittaria sagittifolia *with submerged, floating, and aerial leaves. (From a drawing by E. H. Roberts.)*

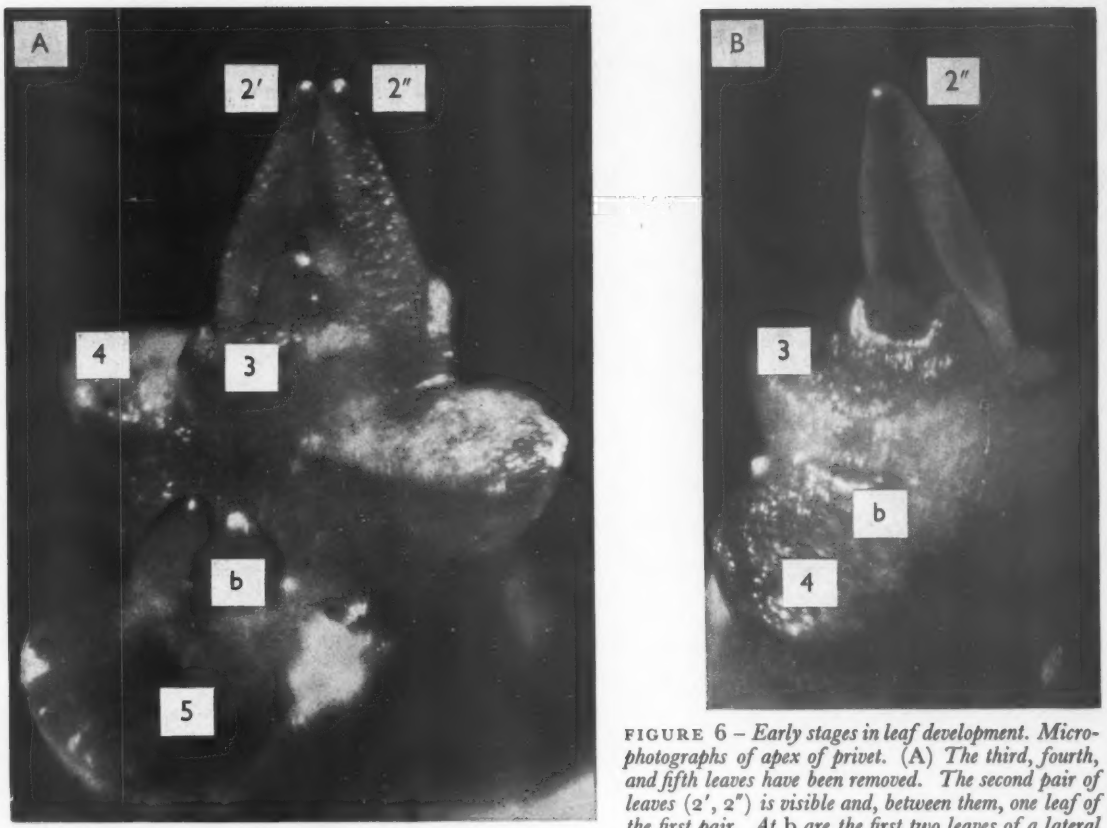

FIGURE 6 – *Early stages in leaf development. Microphotographs of apex of privet.* (A) *The third, fourth, and fifth leaves have been removed. The second pair of leaves* (2′, 2″) *is visible and, between them, one leaf of the first pair. At* b *are the first two leaves of a lateral bud.* (B) *One of the second leaves* (2″) *and the first pair of leaves.* (*Photograph by Dr B. C. Sharman.*)

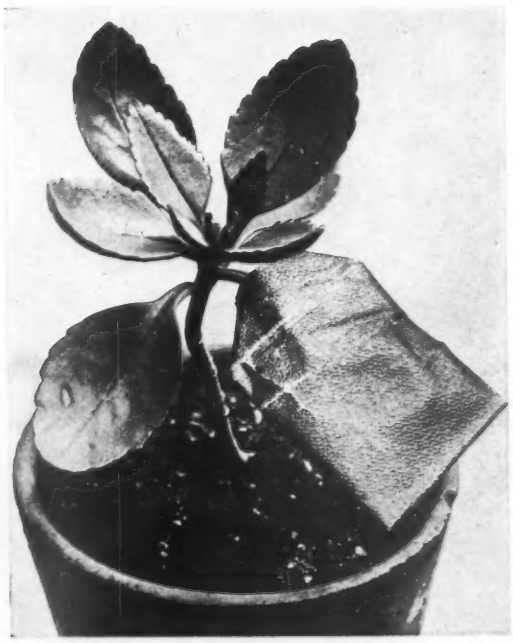

FIGURE 7 – Kalanchoe Blossfeldiana, *with one leaf subjected to nine-hour days. The treated leaf produces a substance which affects the shape of other leaves.* (*Photograph by Ernest Ashby.*)

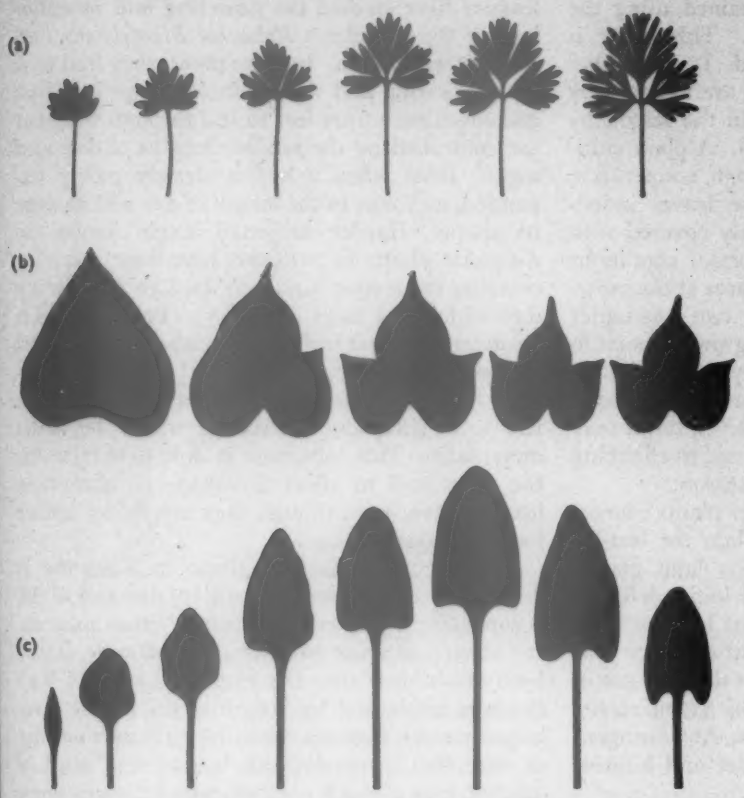

FIGURE 8 – *Successive leaves of* (a) Delphinium ajacis, (b) *morning glory,* (c) *sugar beet.* (*By permission of the Cambridge University Press.*)

number of the node at which the leaf occurs. Here, therefore, is suitable material for the study of pattern in plants—material which varies regularly and quantitatively in genetically homogeneous tissues.

A study of the change in shape from leaf to leaf on a stem raises four major problems. How is shape determined (as it must be) by local differences in cell division and growth? What is the chemical and physical background to these local differences in cell division and growth? By what mechanisms does the environment affect leaf shape? Is leaf shape related to maturity and, if so, can it be used as a measure of physiological age in flowering plants?

There is no prospect of an early solution to any of these four problems, but preliminary results are encouraging enough to justify further work. In the compass of this article only two of the problems will be discussed: the relation of leaf shape to environment, and the relation of leaf shape to physiological age.

The harebell, *Campanula rotundifolia*, has round leaves when young and linear leaves when older (figure 2*a*). Forty years ago Goebel, in Munich, cultivated harebells in very low light intensity and found that they continued to produce juvenile round leaves, even up to the flowering stage (figure 2*b*). This led him to suggest that the linear form of leaf is a response to good nutritive conditions and the round form a response to poor nutritive conditions. In good light Goebel could always produce linear leaves in succession to round leaves, but he failed by any treatment to suppress round leaves while the plant was young. He therefore concluded that the familiar youth-forms of leaves are a reflection of the initially low concentrations of nutrients in young plants. Goebel found that other treatments which deplete the nutrient reserves may evoke round leaves, even in old plants; cuttings, for instance, taken from an adult shoot which bears long leaves, very often revert to round leaves at the beginning of their growth (figure 2*c*). These reactions are not peculiar to the harebell. Juvenile leaves in other plants (for instance in eucalyptus, figure 4) can be evoked by heavy pruning or by cultivation in deep shade. Around these phenomena there grew up the tentative hypothesis that leaf form in many plants responds to nutrition, and in particular to the balance of carbohydrate and mineral salts. It was believed that if carbohydrate is depleted the primitive youth form of leaf is laid down at the meristem. This hypothesis was consistent with the behaviour of some amphibious plants. Certain water buttercups, for instance, produce one sort of leaf in water and another sort in air (figure 3). There is evidence that this response of leaf shape is not due to the air or water medium *per se* but to the fact that the leaf assimilates less efficiently in water than in air. With a high light intensity and a low temperature it is possible to produce air leaves under water, and some workers claim to have produced water leaves in air, the air being damp and free from carbon dioxide.

Similar results have been obtained using the arrowhead, *Sagittaria sagittifolia*. This plant is common in waterways in England. Its first leaves in spring are ribbon-like. These are followed by ovate floating leaves, and later in the season by arrow-like aerial leaves (figure 5). A plant cultivated in deep shade and at a high temperature continues to produce ribbon-like leaves indefinitely, even if the plant is scarcely covered with water. A plant cultivated in normal conditions produces its floating and aerial leaves at the growing-point, which may be one or two feet under water. Leaves dissected from the growing-point in summer, even when they are very small, already have the shape of adult aerial leaves. Leaf shape is clearly not a response to water level, but it may reasonably be regarded as a response to changing nutrient level during the growth season.

This familiar behaviour of water plants cannot, however, be extrapolated to explain the leaf-to-leaf trends in shape among many land plants. Changes of shape of the sort shown in figure 8 take place irrespective of gross nutrient level or light intensity. However, there is recent evidence that it is not the gross nutrient level but the presence of specific growth-form substances which controls the trend in leaf shape in certain plants. At Göttingen, during the last eight years, Harder and his colleagues have studied the flowering and morphology of the succulents *Kalanchoë Blossfeldiana* and *Sedum kamschatkicum*. In these plants they find that both flowering and the gradual change in shape and succulence from leaf to leaf through the year are controlled by the relative lengths of day and night. Even when a leaf is already partly expanded, a change in the length of day will change its shape. Harder subjected single leaves on *Kalanchoë* plants to artificial nine-hour days by covering them from 5.30 p.m. to 8.30 a.m. every day with black bags (figure 7). Following this treatment the next leaf vertically above the treated leaf assumed a 'short-day shape.' Harder interprets this as evidence that short days produce in a leaf some formative substance, which he calls metaplasin. This substance is able to diffuse up the plant and to affect the shape of immature leaves above, even though they are living under long-day conditions.

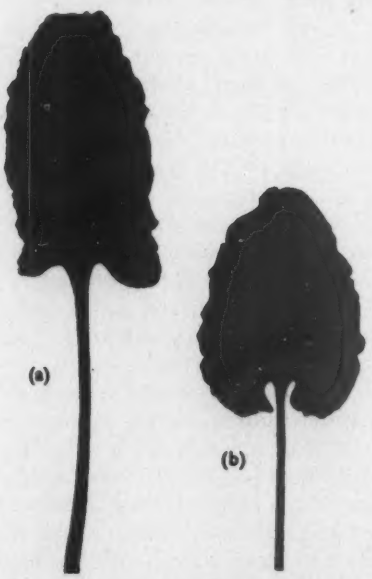

FIGURE 9 – *Sixteenth leaves of sugar beet:* (a) *heavily irrigated,* (b) *unirrigated. Both leaves are about the same time-age.* (*From Minina,* Theory of Cyclic Ageing and Rejuvenescence, *Moscow.*)

The discovery that leaf shape in *Kalanchoë* is dependent on the relative lengths of day and night is consistent with observations from other sources. In cotton (*Gossypium herbaceum*), for example, it has been established that the rate of change of leaf shape is influenced by length of day. The first leaves in some varieties are entire, and the amount of dissection increases from leaf to leaf until a 'climax' type of leaf is reached, which may be very deeply dissected. The time of flowering usually corresponds with the appearance of the climax type of leaf. In varieties with dissected leaves there is a clear connection between the development of dissection at an early node and early flowering: cultural conditions which hasten the one also hasten the other. The number of nodes which bear juvenile leaves is correlated with the duration of the preflowering period of development.

This evident parallelism which has been observed in cotton between the rate of change of leaf shape from node to node and the rate at which sexual maturity is reached led a Russian botanist, N. P. Krenke, to suggest that change in shape of successive leaves might be used to measure physiological age. Physiological age is a familiar but elusive concept in biology. The saying that a man is as old as he feels is sound physiology, yet there is no way to estimate his physiological age quantitatively; his development has to be measured against his time-age. Now the time-age of a plant is not a very useful measure, because a plant grows by localized meristems, and the branch of a tree, for example, may be ten years old at one end and ten minutes old at the other. Therefore any attempt

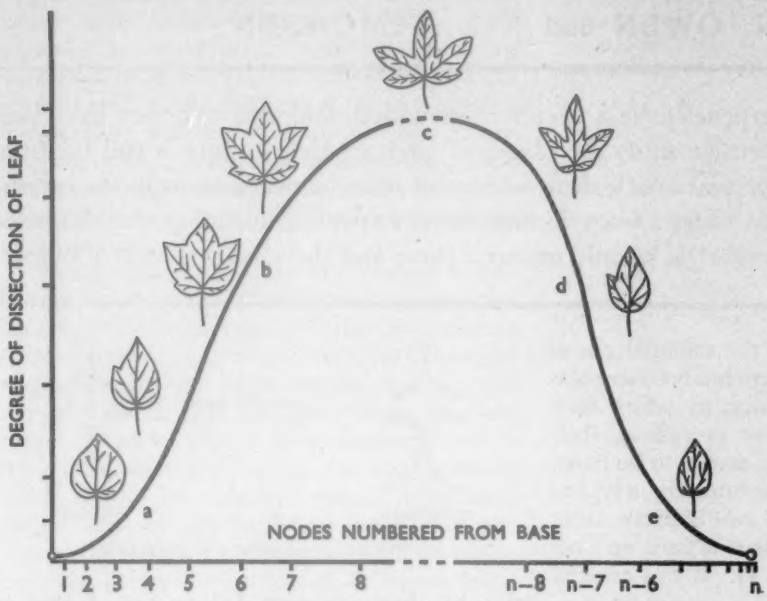

FIGURE 10 – *Diagram to illustrate the use of leaf shape in cotton to measure physiological age. (From a drawing by E. H. Roberts.)*

to measure the physiological age of meristems in plants, however tentative it may be, is worthy of serious attention. Krenke's work is such an attempt.

Using cotton, Krenke plotted the degree of dissection of the first, second, third, etc., leaves on a stem against the node number. He obtained curves of the general shape *abcde* (figure 10). He claimed that the shape of this curve represents the rate of ageing of the plant: the ordinates are the criteria of physiological age and the abscissae are units on a scale of development, as distinct from a time-scale. According to this hypothesis, external conditions which hasten flowering increase the slope of the curve *ab*, and the climax shape *c* is reached at a relatively early node; external conditions which delay flowering decrease the slope of the curve *ab*, and the climax shape *c* is reached at a relatively late node. Plants grown under different conditions may therefore bear leaves on corresponding nodes which have the same time-age but which are of different physiological age. This is exemplified by the sugar-beet leaves shown in figure 9 (from a paper by another Russian worker, Minina). Both leaves were on the sixteenth node and were about the same time-age. Leaf *a* is from an irrigated plant which will not mature early; leaf *b* is from an unirrigated plant which will mature early. On the criteria of leaf shape in sugar beet (see figure 8*c*) leaf *b* is physiologically older than leaf *a*. There is even some indication that the percentage of sugar in the root at any time may be roughly estimated from the shape of the last leaf which has unfolded.

A hypothesis as comprehensive as this cannot be accepted (however promising it appears to be) until something is known of its theoretical basis. There is at present no adequate theoretical basis for Krenke's hypothesis. His results indicate, however, that, among the problems of morphogenesis, the analysis of leaf shape is a problem of special significance. Nineteenth-century botanists have bequeathed us a rich legacy of observations on leaf forms in juvenile plants, amphibious plants, and so on. With twentieth-century techniques it will be possible to extend these observations considerably, and perhaps to extract from them an understanding of the causes and significance of leaf shape.

Some aspects of terpene chemistry

L. N. OWEN and J. L. SIMONSEN

For the organic chemist terpenes have a peculiar fascination, and although they have long received extensive and intensive study the chemical territory they occupy is still far from being fully mapped. The present article deals with some recent developments in the investigation of monoterpenes (as distinct from di- and sesqui-terpenes), including elucidation of the true nature of the odoriferous ketonic material irone and the total synthesis of pinene.

Terpenes are constituents of the essential oils of plants, and for many years there has been speculation on the possible mechanisms by which their biogenesis occurs. With a few exceptions, their chemical structures have been shown to be based on that of isoprene, C_5H_8; thus limonene, a typical monocyclic terpene, contains two isoprene units, while the sesquiterpene cadinene is built up from three such fragments (figure 1). It has recently

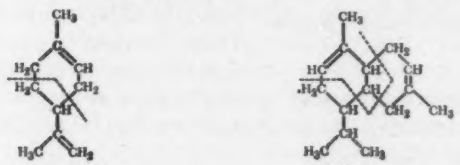

FIGURE 1 – *Isoprene structure of terpenes.*

been suggested [1] that isoprene might be formed in nature from the amino-acid leucine, derived by degradation of proteins, and it is tempting, therefore, to consider isoprene as a possible precursor of the terpenes, particularly since this hydrocarbon has been converted in the laboratory into a mixture of products containing geraniol, linalool, terpineol, sesquiterpene alcohols, and higher polymers [2]; it must be admitted, however, that somewhat vigorous conditions are necessary for these reactions to occur. An entirely different theory of the origin of terpenes [3] suggests that they are formed by condensation of saccharic and metasaccharonic acids, derived by degradation of carbohydrates; here also there is unfortunately little direct evidence to support the speculation. It is abundantly clear, however, that the biogenesis of a key compound, such as geraniol, would be sufficient to account for the formation of a large number of other terpenes, since interconversions can occur under comparatively mild conditions. A striking example is afforded by the recent laboratory synthesis of ascaridole (figure 2);

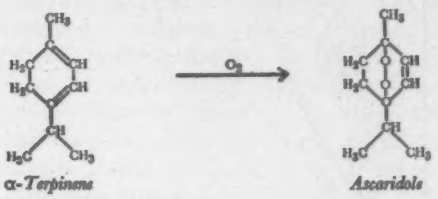

FIGURE 2 – *Synthesis of ascaridole.*

this has been obtained [4] by 1:4-addition of oxygen to α-terpinene, in the presence of chlorophyll and under the influence of ultra-violet light, a process which might evidently be responsible for the occurrence of this remarkable substance in nature. In view of the increasing availability of isotopic materials—particularly of radioactive carbon—it would appear that further advances in this interesting section of terpene chemistry may well result from the use of 'labelled' compounds in studies of plant metabolism.

Since the last decade of the nineteenth century, when many fundamental investigations on the structures of monoterpenes were being made, there has existed the *iso*propenyl—*iso*propylidene controversy over the position of a particular ethylenic linkage in the molecule [5]. It would be anticipated that a clear differentiation between the two structures under discussion, shown diagrammatically in figure 3, could be effected by oxidative degradation, particularly with ozone, when the

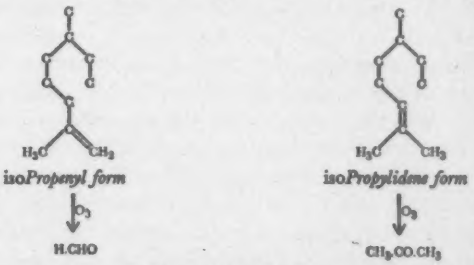

FIGURE 3 – iso*Propenyl and* iso*propylidene structures.*

*iso*propenyl form would give formaldehyde and the *iso*propylidene form would give acetone. Such chemical investigation of naturally occurring citronellal, geraniol, etc., has indicated that these terpenes are actually mixtures of the two isomeric modifications, different samples containing varying proportions, with the *iso*propylidene form usually predominating. Similar results have been obtained even on apparently homogeneous crystalline derivatives.

Physical evidence, on the other hand, is conflicting. In some instances it has been claimed that ultra-violet absorption spectra prove the existence of the *iso*propenyl structure only; in others the results indicate that the particular terpene consists only of the *iso*propylidene form. Measurements of Raman spectra have also been used to prove the homogeneity of, for example, geraniol, though for this particular substance the conclusion that it was the *iso*propylidene form was contrary to the evidence of the ultra-violet absorption spectrum; furthermore, instances are known where deductions from Raman spectra have been completely disproved by later chemical investigations. The interpretations of oxidative degradation have been criticized on the grounds that attack by ozone may not be limited to the ethylenic linkage, but though it is true that side reactions may occur to a small extent, it is highly improbable that they would do so in the degree necessary to account for the proportions of acetone and formaldehyde actually encountered. The most recent physical evidence—an investigation of the infra-red absorption spectra of various samples of citral, geraniol, and citronellol [6]—agrees with the chemical conclusions and indicates the existence of both the *iso*propylidene and *iso*propenyl modifications in the natural oils.

Although the majority of terpenes obey the 'isoprene rule,' there are a number of interesting exceptions (figure 4). Several are now known in which the isoprene units, instead of being arranged in the usual head-to-tail fashion, are joined irregularly; examples are found in lavandulol [7] and in artemisia ketone [8]. The C_{16} ketones angustione and dehydroangustione are built up from two isoprene units with one additional carbon atom [9]. The structure now assigned to leptospermone [10] represents a complete departure from the isoprene rule, and similar exceptions have recently been met in the sesquiterpene field, as shown by the constitutions adopted for eremophilone and its derivatives [11]. The discovery of such anomalies is important, since the structures

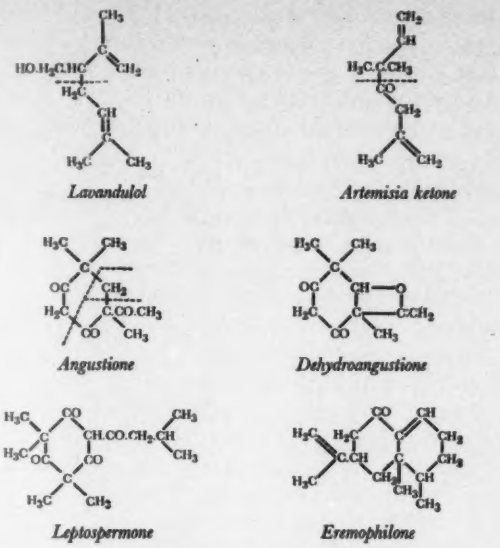

FIGURE 4 – *The isoprene rule: variations and exceptions.*

assigned to several sesquiterpenes have been based partly on the assumption of the validity of the isoprene rule, particularly in instances where the compound contains an 'angular' methyl group, such as, for example, in selinene. It is clearly desirable that the exact position of such angular methyl groups should be established experimentally, and this has been accomplished in the case of cyperone (figure 5) by direct synthesis [12],

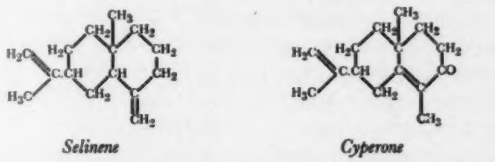

FIGURE 5 – *The angular methyl group in sesquiterpenes.*

thus confirming that the structure of this ketone does conform to the isoprene rule.

One of the most interesting recent developments in terpene chemistry has been concerned with the ketonic material irone, the odoriferous principle of orris root, the chemical study of which has now extended for over fifty years. Irone was originally thought to have the composition $C_{13}H_{20}O$, and although this was shown in 1933 to be incorrect [13] the error was perhaps a fortunate one, since it was largely responsible for the preparation and study of the ionones, the chemistry of which subsequently assumed such importance in connection with the structure of vitamin A and the carotenoids.

Irone is now known to be $C_{14}H_{22}O$, and in 1942 [14] it was formulated as a substituted cycloheptene (figure 6), since on ozonization followed by oxidation with chromic acid it gave ββγ-trimethylpimelic acid. It was realized, however, that

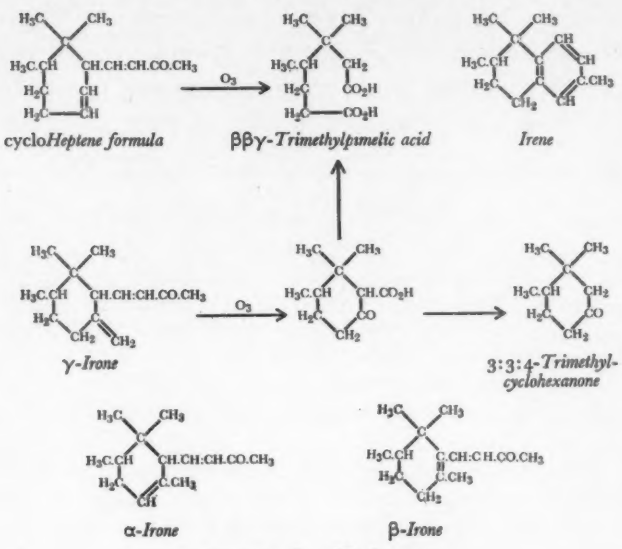

FIGURE 6 – *The irones.*

other ketones might be present in natural irone, for derivatives prepared by different workers frequently showed marked variation in properties; furthermore, it was difficult on the basis of the seven-membered ring structure to account for the conversion of irone into the tetrahydronaphthalene derivative, irene, the structure of which had been definitely established by synthesis. In a recent paper, however [15], describing further investigations on the ozonolysis of irone, it is established that formaldehyde and 3:3:4-trimethylcyclohexanone are products of this degradation, indicating the presence of a ketone with an exocyclic methylene group, now termed γ-irone (see figure 6). It is not unlikely that α-irone also is present, but it is not yet clear whether it occurs as such in the natural oil or is formed by isomerization of γ-irone during the isolation and purification process. The conversion of γ- into α-irone is readily brought about by treatment with weak acids, while with more concentrated acids, or with alkalis, β-irone is obtained.

The α- and γ-isomers possess the characteristic fresh odour of natural irone, the α- form being the more potent; the odour of β-irone, on the other hand, is similar to that of the ionones. α-Irone has now been independently synthesized by two groups of workers [16], an earlier synthesis [17] having given a product which consisted largely of the β-isomer. The formation of irene from either α-, β-, or γ-irone is readily understandable. The evidence for the existence of an irone having the seven-membered ring structure rests solely on the isolation of the trimethylpimelic acid from the oxidation products. Theoretically, it is conceivable that such an acid might be derived, by ring opening, from trimethylcyclohexanonecarboxylic acid, the primary product of the ozonization of γ-irone. If such a transformation could be shown to occur under the conditions employed, it would follow that there would no longer be any reason to postulate the existence of the cycloheptene form. It is significant that tetrahydroirone, obtained by hydrogenation of natural irone, is stated [15] not to be a cycloheptane derivative; it is probably 6-methyltetrahydroionone, but direct comparison with authentic synthetic material is complicated by stereoisomerism.

The problem of the total synthesis of pinene is one which has attracted the attention of organic chemists for many years. It has been attacked from two sides: the regeneration of pinene from its immediate degradation products, and the synthesis of these degradation products themselves. Although progress had been made in both directions, it is only recently that the gap has been closed. Broadly speaking, the investigations have followed two main routes, which are indicated in figure 7. The common starting-point is norpinic acid, a complete synthesis of which was achieved in 1929 [18]; eight years later [19] it was successfully converted into its higher homologue, pinic acid, from which in 1943 [20] pinonic acid was synthesized. The last step completed the synthesis of pinene by this particular route, since the conversion of pinonic acid into pinocamphone, and thence into pinene, had been accomplished [21] about twenty years earlier.

It should be mentioned that the difficulties inherent in these syntheses were intensified by the existence of stereoisomeric modifications of some of the compounds involved, so that the isolation of crystalline products was somewhat uncertain. It is unfortunate, for example, that the synthetic pinic acid could not be induced to crystallize, though it was identified by the formation of a crystalline anilide. From this point of view, the other route has proved to be more satisfactory.

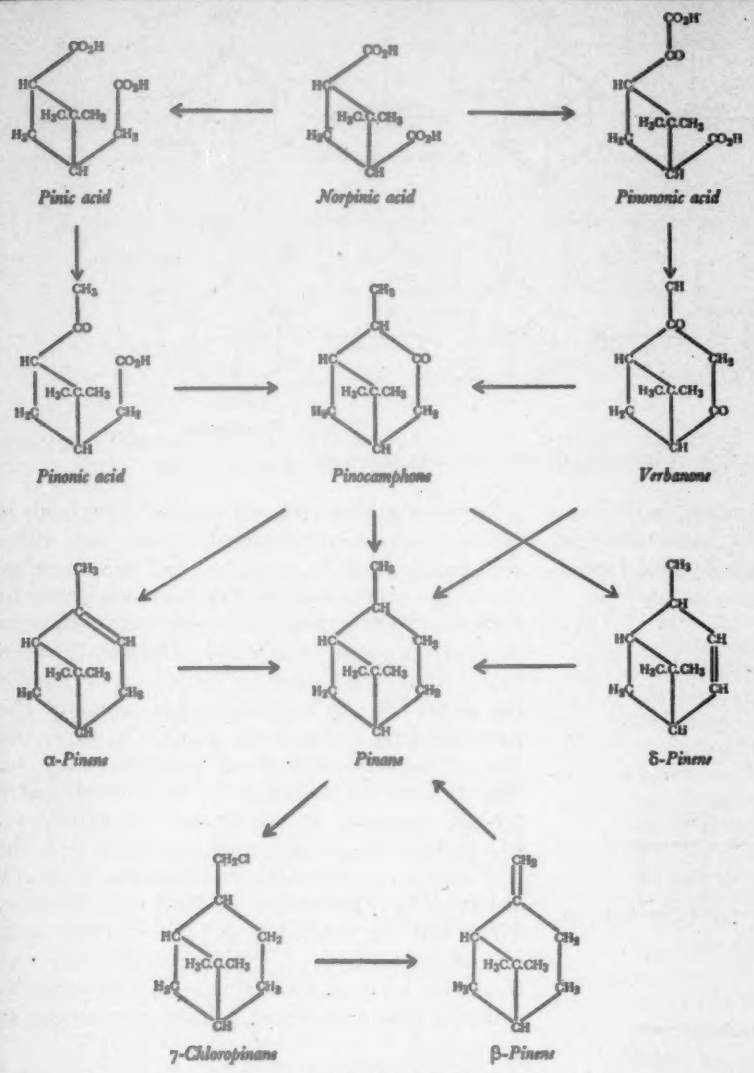

FIGURE 7 – *Synthesis of the pinenes.*

The first step, the synthesis of pinononic acid from norpinic acid, was reported in 1936 [22], and in the following year [23] the keto-acid was successfully converted into verbanone. The transformation of this ketone into the structural isomer, pinocamphone, was accomplished in 1941 [24] by the interesting sequence of reactions illustrated in figure 8, thus completing the last remaining stage in this series of syntheses. The saturated hydrocarbon, pinane, can be obtained by hydrogenation of any of the pinenes, and also by Wolff-Kishner reduction of verbanone or pinocamphone. On chlorination, one of the products is 7-chloropinane (figure 7), which on treatment with potassium phenoxide gives β-pinene (nopinene); this therefore constitutes a complete synthesis of the latter hydrocarbon.

An important synthesis of borneol and *epi*borneol was reported in 1939 [25]. Condensation of 1:5:5-trimethylcyclopenta-1:3-diene with vinyl acetate proceeded in both of the two possible directions; hydrogenation, followed by saponification of the products, gave *dl*-borneol and *dl-epi*borneol (figure 9).

During many reactions in the terpene field, particularly when bicyclic compounds are involved, molecular rearrangements are likely to take place. In earlier days, lack of appreciation of this fact resulted in considerable confusion in the literature and in much controversy between different groups of workers. It was eventually realized that transformations of the pinacolic type occurred under appropriate conditions, and when these led to a change of ring structure, they were classified as examples of the so-called Wagner-Meerwein change. A few examples were also known of pinacolic change without variation in ring structure, such as the formation of santene from camphenilol, but only comparatively recently has it become apparent that this simple isomerization is by no means an infrequent occurrence; it has been termed a camphene change of the second type, but is more usually referred to as the Nametkin change [26]. The appreciation of its existence has had several very important consequences, such as the re-formulation of a number of derivatives in the camphane series, but perhaps one of the most interesting is the explanation it offers of the facile racemization shown by camphene, bornyl chloride, etc., particularly under acid conditions. In the scheme illustrated in figure 10, *d*-camphene is shown to

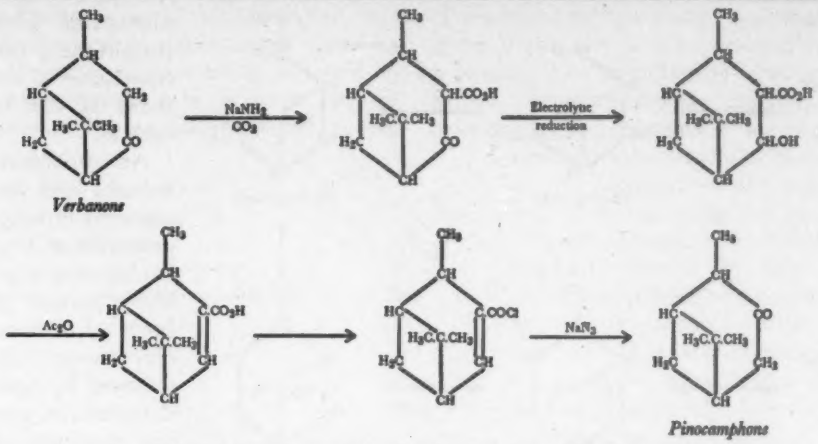

FIGURE 8 – *Conversion of verbanone into pinocamphone.*

give camphene hydrate on hydration; in this substance a pinacolic change of the Nametkin type, resulting in an interchange of the hydroxyl group

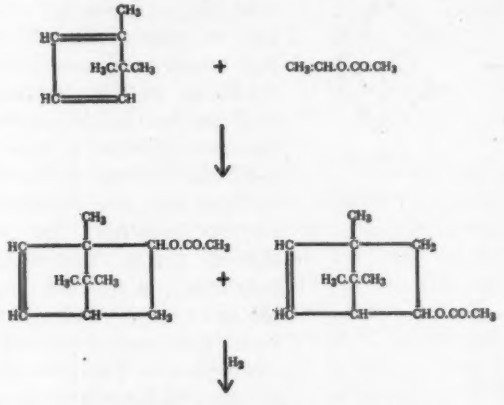

FIGURE 9 – *Synthesis of borneol and* epi*borneol*

with one methyl group on the adjacent carbon atom, results in the formation of a product which is still camphene hydrate, but of opposite stereochemical configuration, i.e. a derivative of *l*-camphene. Clearly, therefore, the camphene isolated from a reaction carried out under such conditions on either *d*- or *l*-camphene will be completely racemized. Similar considerations can be applied to the racemization of camphene in non-aqueous solutions.

In the example just quoted, complete racemization is the ultimate result of the Nametkin change, since the bridge heads are similar and the equilibrium proportions of the two hydrates must be identical. If, however, the bridge carries a substituent at one end, the product, although in the opposite stereochemical series, will differ structurally from its precursor and will therefore not be the enantiomorph. Furthermore, it may be formed in yield greater than 50 per cent., since the equilibrium proportions of the substances involved in the Nametkin change are no longer necessarily the same. By an ingenious application of this principle [27] it has been possible to carry out several interconversions of enantiomorphs (as distinct from racemization) in high yield, and a typical example is illustrated in figure 11. *l*-Camphor, $[\alpha]_D - 43°$, was converted into the α-dichloride, from which α-chlorocamphene was obtained by elimination of hydrogen chloride. When this was treated with trichloroacetic acid, it underwent both the Wagner-Meerwein and Nametkin rearrangements, to give, after saponification, 4-chloro*iso*borneol, which on reduction to

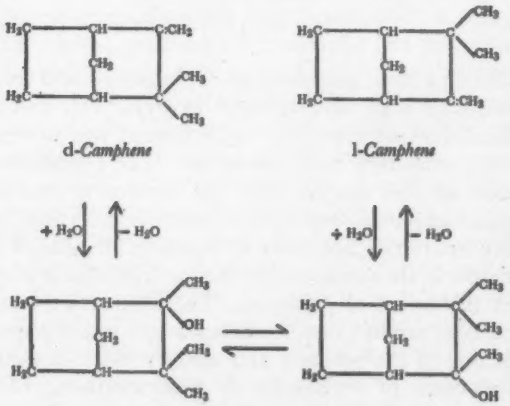

FIGURE 10 – *Racemization of camphene.*

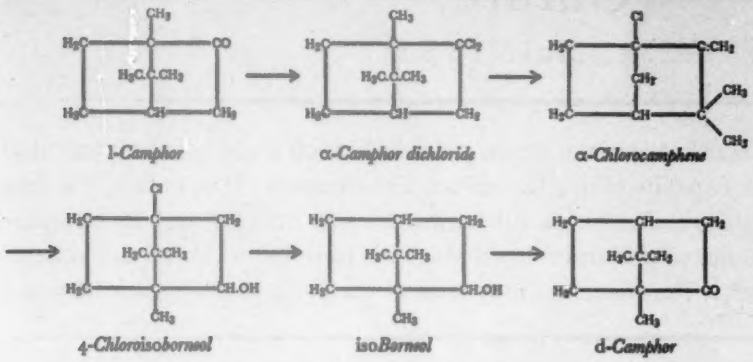

FIGURE 11 – *Conversion of* l- *into* d-*camphor.*

*iso*borneol followed by oxidation gave *d*-camphor, $[\alpha]_D + 32°$. This represents an 'optical conversion' of 74 per cent., the remainder having been racemized.

It has not been possible in this brief survey to refer to the many important developments which have occurred in the fields of sesqui- and di-terpene chemistry, though here, no less than in the realm of monoterpenes, many problems still await investigation. The unabated interest which is still shown in terpene chemistry will undoubtedly ensure continued advance in our knowledge of these fascinating substances.

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Curare

A. R. McINTYRE

Curare, one of the dreaded South American arrow poisons, is such a complex mixture that its analysis proved beyond the capacity of nineteenth-century chemists. It is, in fact, less than fifteen years since the first curare alkaloid, *d*-tubocurarine, was isolated and its structure determined. Biochemical studies of this and related alkaloids have led to important conclusions on motor-nerve and muscle function, and may lead to the conquest of muscle diseases.

The first account of South American arrow poisons was written by Peter Martyr D'Anghera and is found in the first 'Decade' of his *De Orbe Novo*, printed in 1516. These poisons were greatly feared, and with good reason. Inevitably, returning sailors told fantastic tales of the fearsome missiles showered upon them. Peter Martyr collected these stories, and many of them, often repeated by others, gradually became established and were deemed true. Thus it came to be believed that some venoms caused permanent 'hideous distortions of face and body, so horrible that no man could bear to look upon the victims'; others were alleged to produce insanity, 'they going endlessly about beating their heads on the walls' (Garcilasso de la Vega). Sir Walter Ralegh,[1] who is popularly but erroneously supposed to have first brought samples of arrow poisons to Europe, writing of them said, 'the partie shot indureth the most insufferable torment in the world, and abideth a most uglie and lamentable death, sometimes dying starke mad, sometimes their bowels breaking out of their bellies, and are presently discolored, as blacke as pitch . . . ' The ingredients were said to contain 'an underground tuber which flowers in the earth'; 'juices of trees, fangs of serpents, ants, stings of scorpions' (Gumilla), and the 'barke of the Roots of Couranapi, Baketi and Hatchybaly' (Bancroft), besides 'the fabulous coonycoochy snake' (Hillhouse).

The poison of chief interest to scientists was curare. Curare is a generic name of dubious etymology, thought to be derived from the Indian word *urara* or its many variants, some of which are *urali*, *woorali*, and *woorara*. This is the poison the preparation of which was believed for centuries to be watched over by criminal old women of the tribes, 'who are made to take care of the boiling of the poison after shutting them up alone in a separate place so that, when the women die, 'tis a sign that the poison is sufficiently boiled . . . ' (De la Condamine). Curare to the physiologist designates a particular type of poison, which, upon gaining access to the blood, results in a loss of the normal motor-nerve control of the voluntary muscles. It is not surprising that the occurrence of a poison with so specific an effect aroused much interest, and from the eighteenth century until today botanists have sought to establish the identity of the plants used in its concoction. Humboldt was among the earliest to investigate the origin of curare; he believed the plants used were members of the genus *Strychnos* (*Loganiaceae*). Martius described five distinct types of poison, some of which contained specimens of *Cocculus* only. The Schomburgks saw curare prepared from plants identified as *Strychnos toxifera*. Present-day knowledge, briefly summarized, makes it certain that at least two main species, used either singly or together, are employed in the preparation of curare; these are several species of *Menispermaceae* (moonseed family) and *Strychnos*. The latter genus is widely distributed throughout the tropics, and the species *Strychnos nux vomica* of Asia is well known as the source of strychnine—an entirely different type of poison.

The botanist's task is formidable because, as is natural with primitive peoples, the Indians seek to surround the making of curare with mystery. They prepare it in the jungle at some distance from their villages and, contrary to legend, do not allow any female to come near the place of preparation. They mix many relatively inert ingredients with those that are active: some of these are certain plants and herbs (*Moraceae*, *Rutaceae*, etc.) said to be rich in gums and resins, which impart physical properties to the aqueous infusion such that it will adhere to the tips of the darts and arrows. The crude native product is a blackish-brown sticky mass with a characteristic odour, containing from 5 per cent. to sometimes as much as 17 per cent. of

[1] Sir Walter usually spelled his name without the 'i'.

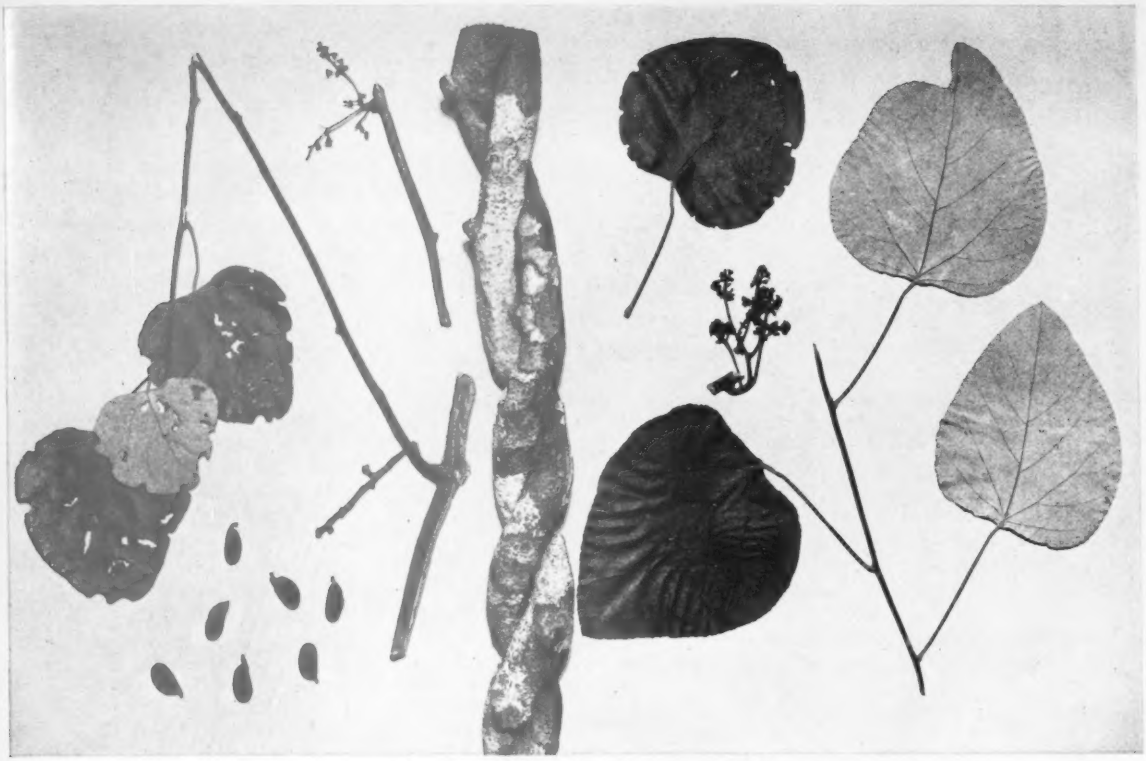
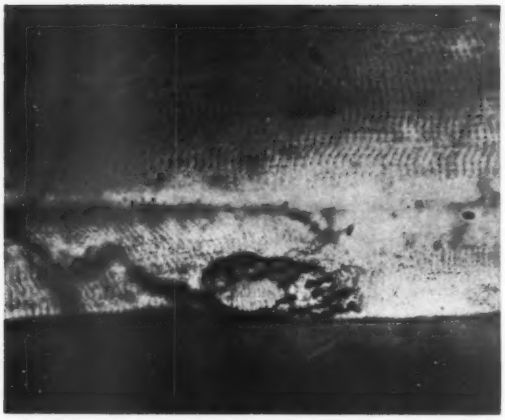


FIGURE 1 – *Leaves of* Chondodendron tomentosum *and a piece of the rope-like vine.*

FIGURE 2 – *This illustration shows the native container (top, left) for the cotton which is placed on the blunt end of the dart just before use. The crude curare is usually smeared on the darts and allowed to dry and is sometimes moistened just before use. The other container (bottom, left) contains crude curare.*



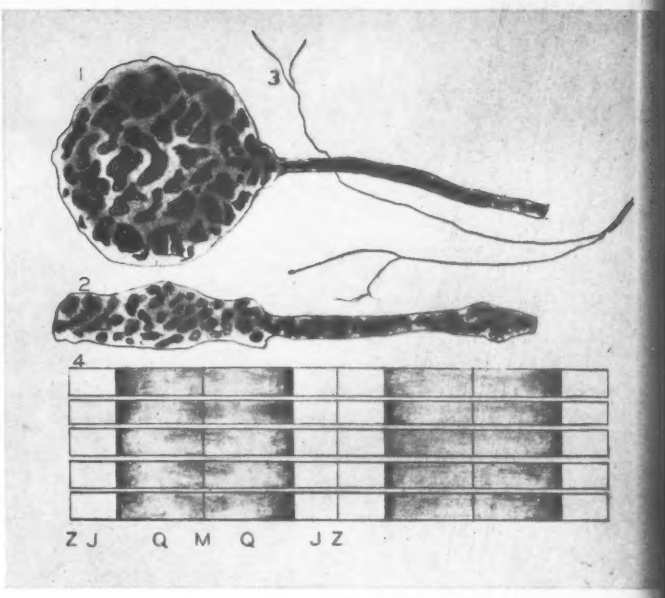


FIGURE 3 – *Photomicrograph (above) of rat striated muscle, showing motor nerves, end plates, and muscle striation. On the right are shown:*

1. *Diagram of motor nerve end plate.*
2. *Same as* 1, *but turned through* 90°. *The end plate contains a lipid material which stains black with gold chloride.*
3. *Small motor nerves with no end plates.*
4. *Conventional diagram, showing the detail observable in the cross-striation of skeletal muscles. Muscle consists of elongated fibrils, a portion of five such fibrils is shown with their characteristic alternating dark and light bands. The darker bands seen under polarized light are doubly refractive (anisotropic); the light bands are isotropic. Rollett designated the dark bands by Q, the light bands by J. A fine membrane Z can be discerned in the light band. When the muscle is contracted the dark bands (Q) become wider. The point of action of curare is at the junction between the nerve endings and the muscle fibrils.*

Diagrams 1, 2, *and* 3 *are drawn about* $\frac{1}{16}$ *the scale of diagram* 4.

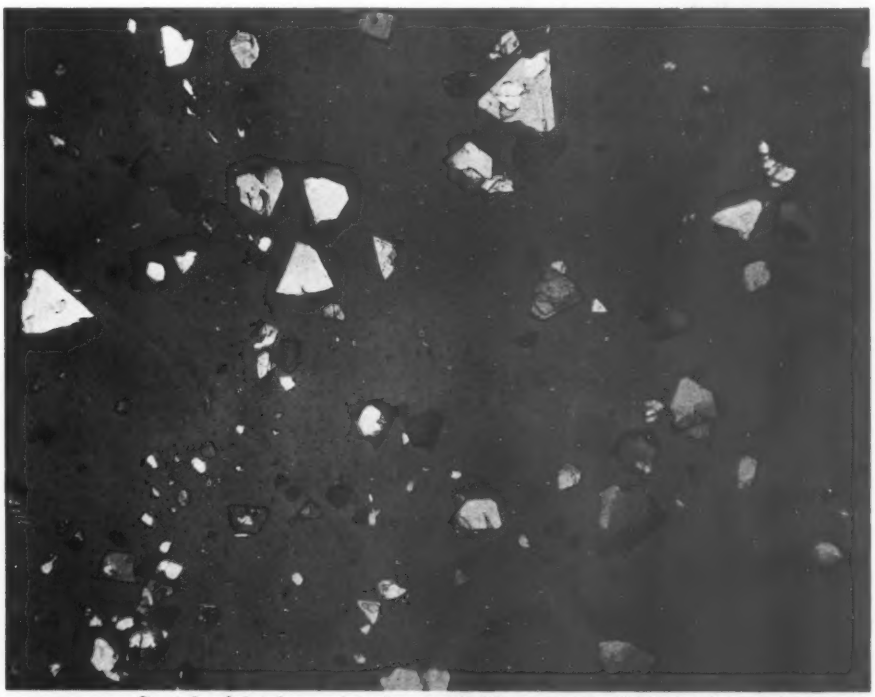


FIGURE 4 – *Crystals of* d-*tubocurarine photographed between crossed Nicol prisms, using a half-wave plate.*

d fibrils;
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alkaloids in the relatively inert mixture of saponins, carbon particles, and other extraneous matter. This mixture has frequently and with justice been described by the analytical chemist as 'difficult,' and the physical nature of curare largely accounts for the failure of early investigators, such as Boussingault (1827) and Pelletier and Caventou (1829), to isolate the pure alkaloids. In fact, it was not until the publication of King's work in 1935, on the isolation of *d*-tubocurarine from tube curare, that the chemical structure of the curares was established.

This was some forty years after Boehm had shown that curare contains two chief types of physiologically active alkaloids. The first, causing muscle paralysis, he named 'curarines'; they are quaternary bases. The second, which have direct effect on the blood-pressure, are tertiary bases; these he called 'curines.' It was Boehm who divided curares into three groups according to the container used by the natives—tube curare in bamboo tubes, calabash curare in gourds, and pot curare in earthenware pots. Today these distinctions are no longer reliable, and most of the large amount of crude curare that has arrived in my laboratory has come in old tins, sometimes with widely known trade marks still visible upon them. In America, Wintersteiner and Dutcher confirmed King's structure for *d*-tubocurarine and isolated it from a sample of *Chondodendron tomentosum*. It is a *bis*-benzoyl*iso*quinoline compound containing two phenolic groups. A number of closely related alkaloids have been obtained by King and also by Wintersteiner and Dutcher from other menispermaceous plants, e.g. *Ch. platyphyllum*, *Ch. microphyllum*, and *Ch. candicans*, and 'pareira brava.' The nature of the alkaloids in pot curare is still obscure, but they are possibly similar to the toxiferins and curarines obtained by Wieland and his associates from calabash curare. Wieland's work is noteworthy because he used an aluminium oxide adsorption column to isolate the alkaloidal Reineckate salts and the chromatographic method for their purification.[1] Of the alkaloids obtained, the toxiferins give a red colour with nitric acid, and the curarines a green and a violet colour with nitric and hydrochloric acids respectively.

Toxiferin I ($C_{20}H_{21}N_2,H_2O$, $[\alpha]_D^{20°} - 610°$) has extreme toxic potency: 0·3 grn is said to be sufficient to paralyse a frog. Two other curare alkaloids named strychnolethaline ($C_{22}H_{27}O_4N$) and curalethaline ($C_{25}H_{30}O_4N$) were isolated by Berrêdo-Carneiro from two samples of curare, and also from *Strychnos lethalis*. He found that they exhibited characteristic spectrographic absorption bands with peaks at 466 and 557 A for curalethaline and 559 A for strychnolethaline. With the exception of *d*-tubocurarine very meagre quantities of pure curare alkaloids are as yet available, and little beyond the fact of their high toxicity is known concerning them. Consequently nearly all the more precise physiological and pharmacological investigations with curare alkaloids have been made with *d*-tubocurarine or with curarines; the exact chemical nature of the latter is unknown. *d*-Tubocurarine is less potent than the toxiferins but produces a true curariform effect, i.e. it is capable of producing paralysis of skeletal muscle without significant direct effect upon the blood-pressure and respiration.

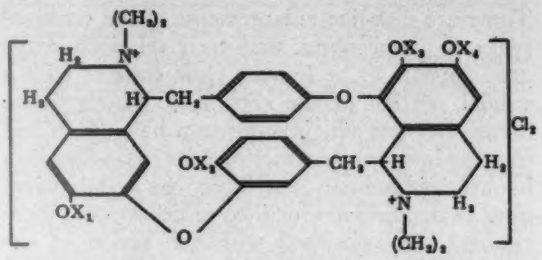

FIGURE 5 – *Structure of* d-*tubocurarine and related alkaloids.* (*Redrawn from Wintersteiner and Dutcher.*)

I. d-*Tubocurarine chloride:* $X_1 = CH_3$; $X_3 = H$; *of* X_3 *and* X_4, *one is H, the other* CH_3.

II. d-*Chondrocurine dimethochloride:* $X_1 = CH_3$; $X_3 = H$; *of* X_3 *and* X_4, *one is H and the other* CH_3, *but in an arrangement which is the reverse of that in I.*

III. d-*Tubocurarine dimethylether iodide:* $X_1 = X_3 = X_3 = X_4 = CH_3$; *anion* $2I^-$ *instead of* $2Cl^-$.

Ever since the classical experiments of Claude Bernard the precise mechanism of curare paralysis has been the subject of controversy, and, though the centennial of Bernard's work will soon be celebrated, no final agreement has yet been reached. The fundamental truth of Bernard's conclusions has never been seriously challenged. He showed that the poison does not affect conductivity in motor nerves or prevent the muscle from responding to a *direct* stimulus; the paralysis in a curarized animal is due to the inability of a motor-nerve impulse to stimulate the muscle. These observations very naturally focused attention upon the nature of the junction between motor nerves and muscles, and as a consequence the so-called motor end plates of nerves were discovered.

[1] For a description of the adsorption column technique, see a recent article in ENDEAVOUR by A. J. P. Martin (Vol. VI, 1947, p. 21).

These are disk-like enlargements of the terminal twigs of motor fibres, and their relatively large area appears to be in very close contact with a special portion of the contractile muscle tissue. Some, but not all, investigators have described changes in the appearance of these plate-like disks in curarized animals, and those who found alterations in the disks are inclined to believe that these changes are associated with the action of the poison. The changes can, however, be produced by many other substances; they are not specific to curare.

In addition to the discovery of the motor-nerve end plates, much physiological knowledge developed as a result of the investigation of toxic substances, and the study of curare has been directly or indirectly responsible for most of what we know concerning the nervous control of skeletal muscle. Thus the examination of the electrical irritability of nerve and muscle has resulted in the Lapicques' theory of chronaxie. This theory is based on the following considerations. When the negative pole of an electrical circuit is placed in contact with an excitable tissue and a current is applied, it will be found that the current, if made sufficiently small, fails to stimulate the tissue no matter how long it is applied. The smallest current capable of producing an effect is the 'rheobase' for that particular tissue. If now the rheobase current is doubled, the time necessary for the current to be applied in order to stimulate the tissue is relatively short; this period the Lapicques call *la chronaxie*; it is found to be constant for a given tissue. According to the Lapicques, nerves and the muscles they control have chronaxies approximately equal, i.e. they exhibit isochronism, but after poisoning with curare the muscle chronaxie is increased; hence the nerve and muscle exhibit heterochronism, and when heterochronicity is sufficiently marked the muscle will not respond to a nerve impulse. This theory of the Lapicques has been most fruitful in the promotion of carefully performed physiological experiments on the irritability of tissues in general, and notwithstanding the fact that the theory of isochronism has met with criticism and is by no means universally accepted, the Lapicques' work is of great importance, if for no other reason than that it provoked wide interest and very extensive studies of nerve and muscle electrophysiology.

The discovery by Langley that curare would prevent nicotine from producing contractions in both normal and denervated frog muscle was of much greater significance than was realized some forty years ago. His receptor theory paved the way for Loewi's investigations on the nature of vagus inhibition of the heart and the discovery that such inhibition was mediated by a chemical factor, namely acetylcholine. This compound makes its appearance as a consequence of vagus nerve activity. Subsequently the role of acetylcholine in nerve-muscle transmission was examined by Dale and others, who found that when motor nerves to skeletal muscles are stimulated acetylchloine can be detected in the fluid perfusing the muscle. It soon became apparent that curarization could be explained by assuming that curare interfered with the effect of acetylcholine on the muscle. Recently Kuffler and Gerard have shown that some of the skeletal muscles of frogs are controlled by two distinct types of motor nerves; the larger nerve fibres appear to be responsible for quick movements of the muscles and the smaller fibres cause steady muscle contraction or 'tone.' Significantly, the smaller nerves do not appear to terminate in end plates. It is known that mammals, including man, also possess at least two types of motor nerves. Curare prevents muscle excitation by the small fibres more readily than it interrupts excitation by the larger nerve fibres. Thus, the muscles supporting the head in an animal such as a rabbit are normally in a steady state of tonus, and these muscles are rather quickly paralysed by curare. On the other hand, during life the muscles of the diaphragm are in almost constant motion, and these are not, at first, noticeably affected by curare. Advantage is taken of these facts in the use of the rabbit as a test animal for the bio-assay of curare preparations. The test is known as the rabbit head-drop test, and was first used by Holiday.

After the use of curare by Sewell for the treatment of tetanus in horses, in England, curare was first used in human tetanus by Sayres, in New York, in 1858. Although curare has been used from time to time in man for a variety of conditions ever since, it is only quite recently that sterile standardized preparations have been readily available, and the modern use of curare in the clinics began with the work of West in England, Griffith in Canada, and Burman, Denhoff, and Bennett in America. Today curare is used very widely and is found particularly useful as a means of increasing muscle-relaxation during anaesthesia. For example, a patient lightly anaesthetized with cyclopropane may be given an intravenous injection of a standardized curare preparation, when the abdominal musculature will promptly relax, rendering the viscera accessible.

Deep anaesthesia is thus avoided, thereby adding considerably to the safety of the patient. Ether has been shown to possess a curare-like action, so when curare is used in ether anaesthesia the dose of curare must be reduced to less than half that used with cyclopropane. The use of curare in dislocations also greatly facilitates the surgeon's task. In such cases there is nearly always strong reflex spasm of the muscles, which necessitates the application of considerable force to relocate the articulating surfaces of the joints involved. The use of curare renders such manipulations relatively easy, and as the muscle spasm is abolished the pain is markedly reduced.

The use of electric shock therapy for the treatment of certain types of psychotic patients is sometimes complicated by injuries suffered during the electrically produced convulsions. Today in many psychiatric hospitals curare is used as a matter of routine to prevent muscle, tendon, ligament, and bone injuries formerly encountered. The use of curare in the treatment of chronic spastic states was carefully examined some years ago by West. The recent fundamental physiological work of Kuffler and Gerard indicates that the use of curare in such conditions has a theoretically sound basis, and this work may lead to an explanation of the early discoveries of Bremer, who described a decrease in the hypertonicity of muscles in decerebrate animals when injected with curare. Similarly the effect of curare in parathyroid tetany, described by Hartridge and West, is rendered more understandable. The effects of intravenous injections of aqueous solutions of curare are somewhat transitory; hence, in the treatment of chronic spasticities, oil and wax suspensions of the alkaloid *d*-tubocurarine have been utilized which, when injected intramuscularly, are absorbed sufficiently slowly to enable a moderate degree of curarization to be maintained for as long as seventy-two hours. Such preparations containing *d*-tubocurarine, or possibly, in the future, other related alkaloids, may prove of value in chronic spastic diseases.

Contrary to general belief, the clinical use of *d*-tubocurarine, or preparations such as Intocostrin, which was first prepared in the author's laboratory and which contains *d*-tubocurarine, is not attended with much risk, because, should the safe dose be accidentally exceeded, artificial respiration and the prompt injection of the antidote neostigmine will at once overcome the paralysis. Hence it is customary to have neostigmine at hand when curare is used. However, some types of curare preparations, particularly those containing certain toxiferins or curarines, are likely to be dangerous because of their effect on smooth muscle, particularly the bronchial musculature. Much interest has been aroused by the discovery that the muscle disease *Myasthenia gravis* renders a patient very sensitive to curare; such patients can tolerate only a fraction of the normal dose. It is of considerable significance that neostigmine, the most effective drug in this disease, is also by far the best antidote for curare poisoning. Hence some investigators suspect that the disease *Myasthenia gravis* may be caused by a substance having a curariform effect. The source of this substance is unknown.

Figures 1, 2, and 4 by courtesy of Dr H. S. Newcomer of E. R. Squibb and Company, New York. Figure 3 by courtesy of the Department of Anatomy, University of Nebraska College of Medicine, Omaha, Nebraska.

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Some aspects of modern laboratory design

J. YULE BOGUE

The design of a new laboratory is of great importance, for under modern conditions of highly specialized work the building must be looked upon not merely as providing accommodation for the research workers but as an integral part of their permanent equipment. Apart from the usual services, special facilities may be needed. Thus biologists and medical workers may require animals for experimental work; research on viruses and infectious diseases may require elaborate arrangements to prevent infection of staff and experimental animals.

The modern research laboratory, besides housing the research worker and his apparatus, should be considered as forming part of his equipment. It is unfortunate that this most essential part of his research facilities has not, until the last ten or fifteen years, received as much specialized attention and investigation as has been devoted to other aspects of his work. Perry Coke Smith (1947) points out that the organization of laboratory space and its mechanical services into a smoothly functioning and easily maintained whole has generally been provided for the research worker by independent authority, rather than in response to his demands.

Although it is not possible to lay down a universal specification for a research laboratory, a study of the more recently constructed academic, government, and industrial laboratories reveals a remarkable similarity in the basic requirements, in spite of a wide range of specialized activities. This is borne out by the general acceptance of the repetitive space pattern or module system. The module may be defined as the minimum space within which a single worker can carry out his research, and which therefore contains within itself all service outlets and points, illumination, ventilation, and other direct services which are brought to the work area.

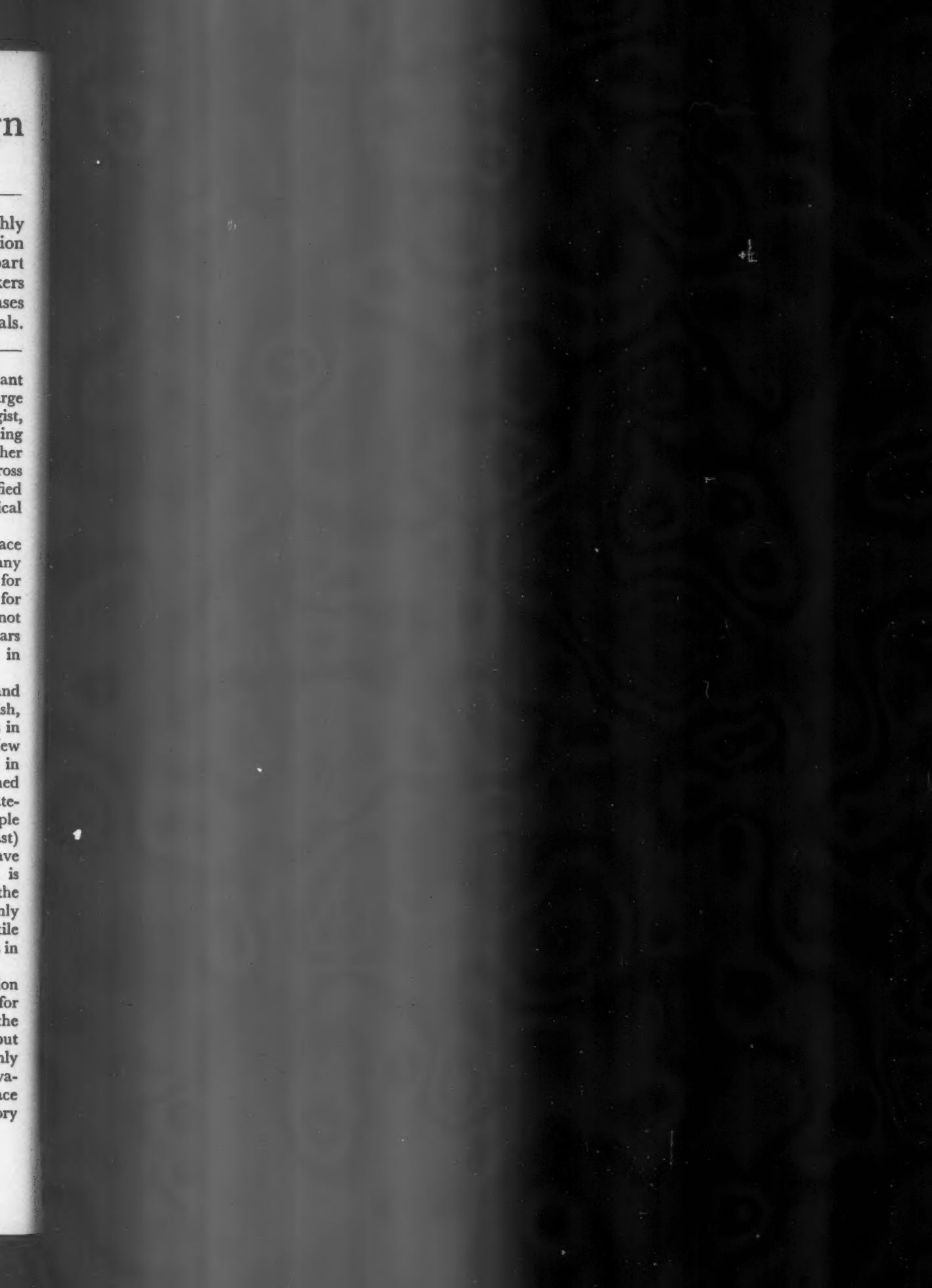
While the dimensions of the module may vary in different laboratories, there is fairly close agreement on the amount of space which should be allocated to each qualified worker. The average figure appears to be around 280 square feet per man. This area includes the floor area (free and covered) available to the research worker. It excludes corridors, stairways, toilets, library, store and workshop facilities, and all other indirect services which are not available at the bench.

A gross area of the order of 500 square feet per qualified man would seem to cover most research activities other than those requiring pilot plant facilities and other specialized equipment of large size. In assessing the gross area for a biologist, animal houses, isolation areas, and sterilizing facilities have to be considered. These and other requirements may involve an increase in gross area up to 2,500 square feet or more per qualified man, depending upon the type of work. Biological facilities of this type are considered below.

The module ensures that this minimal space may be used as a one-man laboratory, while any multiple of the module-width can be utilized for laboratories of different sizes, thus making for maximum flexibility. The one-man module is not often used; a two-man module laboratory appears to be the more usual minimum, particularly in industrial laboratories.

The module partitions are non-structural and are usually made of hollow tile with plaster finish, of terra-cotta tile with semi-glaze finish, or, as in the case of the Bell Telephone Laboratories, New Jersey, of movable steel partitions constructed in sections. The steel panels are of double-sheathed construction packed with sound-absorbent material. These panels can be erected at any multiple of six feet. In Britain, plastic partitions (Holoplast) are being tried. Steel or plastic partitions have the advantage of extreme flexibility, since it is possible to remove and re-erect them with the minimum of interference and with the aid of only a hammer and screwdriver. The removal of tile or plaster partitions, though practicable, results in much dust and disturbance during the process.

There is a considerable difference of opinion with regard to the provision of office facilities for the worker at the bench. From his viewpoint the ideal location is immediately adjacent to, but separated from, the actual work area. The only way in which this can be achieved, with preservation of maximum flexibility, is to partition space primarily designed and serviced for laboratory



purposes. This enables the office to be located anywhere in the laboratory wing and relocated at any time. A more economic use can be made of the space if, for example, the part on the window side is allocated to office purposes, while that on the corridor side is used for others.

Such a layout is shown in figure 1, which is of the standard laboratory unit adopted by the U.S. Department of Agriculture at their Western Regional Research Laboratory. This laboratory module is 16 feet wide by 24 feet deep, with a floor-to-ceiling height of 10 feet 4 inches. The unit is made up of three such modules, namely two laboratories, each of one module, separated and served by a central module divided into two 8 by 13 foot studies on the window side and an 11 by 16 foot utility room on the corridor side. The partitions within the central module are of portable steel units. The utility room can be used for a variety of purposes, such as constant-temperature room, microscopy room, Kjeldahl area, and so on. On the basis of two qualified men per laboratory, this unit provides a working area of 288 square feet per man.

Such a type of laboratory suite can, of course, be extended to serve several laboratories. In this case the junior workers would have their desks in the laboratory. The number of qualified people occupying the office should not exceed two; single occupancy is preferred. The laboratory office should, if possible, have a transparent panel through which the occupant can observe the activities in his laboratory. Where such individual or two-man offices cannot be provided, the worker at the bench should have in his laboratory a desk, a filing cabinet, and some enclosed bookshelves. This is more desirable than an office in a short wing, or at the end of a laboratory wing relatively remote from the work area.

The laboratory office, of whatever type, is not necessarily the area in which the research worker will do his hard thinking. Such work requires close contact with the literature, so that the above facilities must be supplemented by the provision of study rooms in the library area. While engaged in this type of work the research worker should be given sole occupancy for several days, or, if necessary, even for a few weeks.

The generally accepted services include hot and cold water, steam, gas, air, vacuum, and electricity, both single and three-phase. Most laboratories now provide distilled water in block tin or aluminium pipes to single points in each laboratory, or to selected central points in corridors, by gravity feed from a pair of central stills. The risk of contamination, however, may deter the provision of this service. In the interests of reliability it is necessary to carry out regular conductivity tests every few days. As distilled water is an expensive service, the outlet valves should be spring-loaded.

Since the highest possible density of outlets in the laboratory is desired by the research worker, they should be in groups at close intervals. A considerable economy in respect of the main service capacity and loading can be effected by previous study of the number of outlets in use at any one time in a number of different laboratories. The actual number in use at any one time may be considerably less than 10 per cent. of those provided.

It is undesirable to trundle gas cylinders into laboratories. The cylinders should either be housed and connected to local laboratory lines in specially designed cylinder cupboards within the corridor service walls, with access from the corridor only, or be kept on such balconies as have been provided for escape and shade purposes. In this case access to the balcony should be from landings and not through the laboratories. In large laboratories, nitrogen may be supplied from nitrogen cylinder trailers connected to manifolds outside the building.

Except in physical, electrical, and other special laboratories, low voltage (from two volts upwards) and D.C. are not universal. Some workers state that while the D.C. and low voltage are a convenience, it is an expensive one; single- and three-phase supply are, however, essential.

The service piping, conduits, and lines, whether they be vertical or horizontal, on external walls or within corridor walls, need no longer be exposed to ensure accessibility; removable panels or proper doors in corridor walls give adequate access. The essential feature of the service layout is that any of the services may be modified or changed without interrupting the services of adjacent modules. The piping, conduits, and outlets at the bench should be removable. They may be hung on the walls above or below bench height, or on racks which are readily removed. This latter method is used at the Shell Development Company's laboratories, Emeryville, California.

The lighting intensity in different laboratories varies from about 15 to 38 foot-candles. The research worker prefers an intensity of some 30 foot-candles. Lighting by fluorescent tubes in

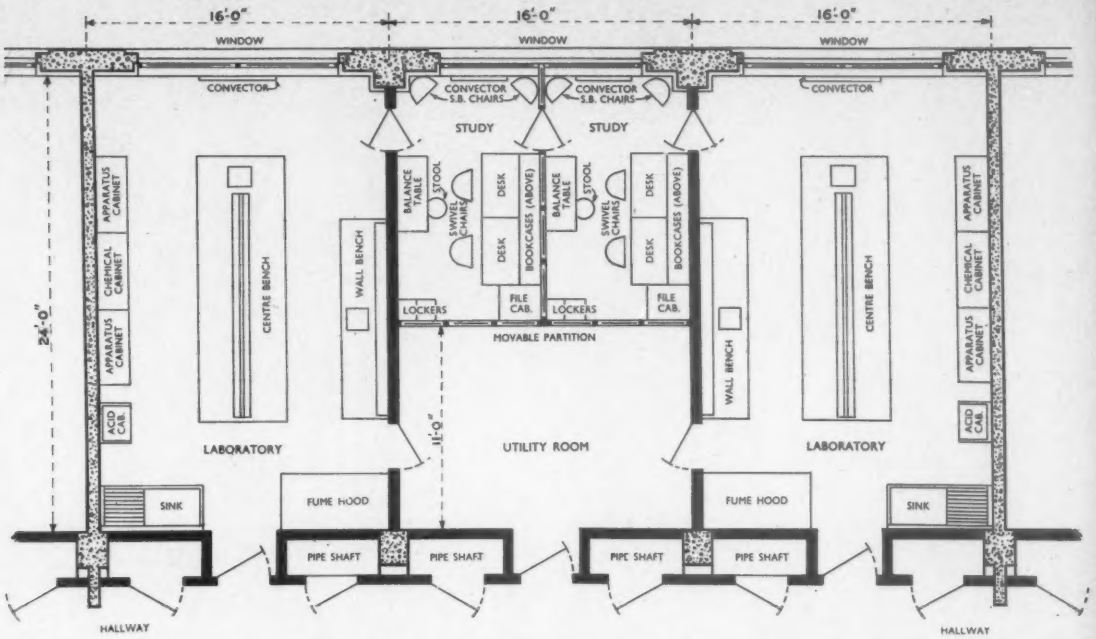


FIGURE 1 – *Standard laboratory unit, Western Regional Research Laboratory, U.S.A.*

recessed fittings is most favoured. It is considered desirable to fit diffusers, preferably of plastic as a protection against accident.

Where fume hoods are necessary, they should have individual fans controlled from the hood of origin. It is an advantage to have one half of the work table removable by the chemist to permit the ventilation of taller equipment. The provision of a ventilated area as well as a proper fume hood is also useful.

All are agreed on the advantages of a completely air-conditioned laboratory. This is expensive, however, as recirculation is out of the question and the fume hoods carry a large volume of treated air away. Beach (1947) believes that this latter problem has been solved by a new 'pressurized' or induced draught hood as fitted in the recently completed B. F. Goodrich laboratories. Air-conditioning is essential for micro-analytical and other special-purpose laboratories. Forced ventilation with filtered and washed air should be provided where air-conditioning is not installed. As constant-temperature rooms are necessary in biological laboratories there should never be less than one hot and one cold room per floor. It has been suggested that an equivalent area of one module in every twelve should be set aside for this purpose.

The module system logically demands an assembly of movable standardized sectional units such as table, cupboard, and drawer. These are usually made of steel, which is protected by lead-flashing the copper-loaded metal, or by some other rust-preventing process, and finishing them with baked enamel. The Mellon Institute uses a demountable metal framework, the components of which are fitted firmly together without the use of bolts or screws. The only tool required for erection or demounting is a rubber mallet. The framework supports the bench tops and sinks, and accommodates the cabinets and drawer units. Bench tops may be of wood, soapstone, plastics, or stainless steel. The recent developments in plastics have opened up a wide range of properties, finishes, and colours.

There is as yet no ideal floor covering; those most commonly used are battleship linoleum, asphalt tile, rubber, and cork, all of which are readily repaired. Quarry tile and concrete are not favoured by those standing at the bench.

While the biologist and medical research worker can carry out most of their activities in suitably arranged modules, they require additional and specialized facilities for their experimental animals. Even in a single institute these facilities may require the provision of properly

designed and serviced areas to house insects, aquaria, mice, rats, rabbits, guinea-pigs, cats, dogs, and monkeys. In some cases there may be many of the larger domesticated animals. These requirements add considerably to the gross space allocation per man. Omitting the larger domesticated animals, the ratio of gross animal house area to laboratory area seems to vary between 1·7 : 1 and 0·7 : 1.

Apart from the problem of special isolation quarters for virus and highly infectious diseases, opinion is approximately equally divided on the desirability of housing the animals in the laboratory building as opposed to an entirely separate building. Where animals are kept in the laboratory block, the majority of workers are in favour of segregation, either by devoting a strategically placed floor to animals or by double air-lock isolation on several floors. It is not considered desirable to mix animal rooms and laboratories. Where the animal need not be brought into the laboratory, the ideal solution appears to be a separate animal block provided with special manipulation and operation areas. In addition to the animal quarters proper, the facilities must include reception, quarantine, and treatment areas for imported stock, sterilizing equipment for bedding, food, cages, and utensils, incineration for bedding and animals, diet-mixing areas, kitchens, and cold stores.

There appears to be a general agreement that air-conditioning with local temperature control and boost heaters is the ideal method of achieving standard environmental conditions. There must be no partial recirculation of air. Laboratories which are not air-conditioned usually provide local equipment for the rat and mouse breeding units. The animal room surfaces must be capable of withstanding hot washdowns at intervals.

While it is not possible within the scope of this article to discuss the details of animal houses and biological laboratories, the special facilities required for investigations into virus and highly infectious diseases should be mentioned. The National Institute of Health's Virus and Infectious Diseases Laboratory at Bethesda is an example of a highly specialized occupancy problem. Every precaution has been introduced to prevent infection of workers and cross-infection of animals. The building consists of three laboratory floors proper, each of which consists of two identical laboratory wings served by a central 'clean' area. The working of the unit is dependent upon a complex air-conditioning equipment, which maintains the air pressure at a higher level in the central clean area than in the laboratory wing, where in turn the corridor air pressure is higher than that of the animal rooms and laboratories. Air supplied to certain areas, such as the sterile cubicles, is irradiated with ultra-violet light and

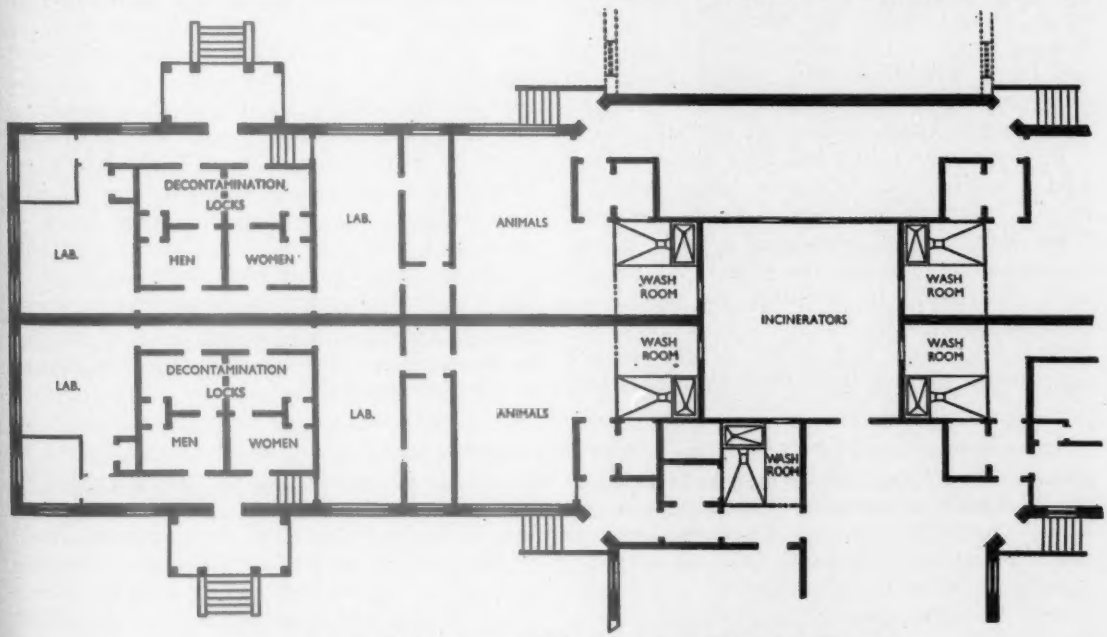
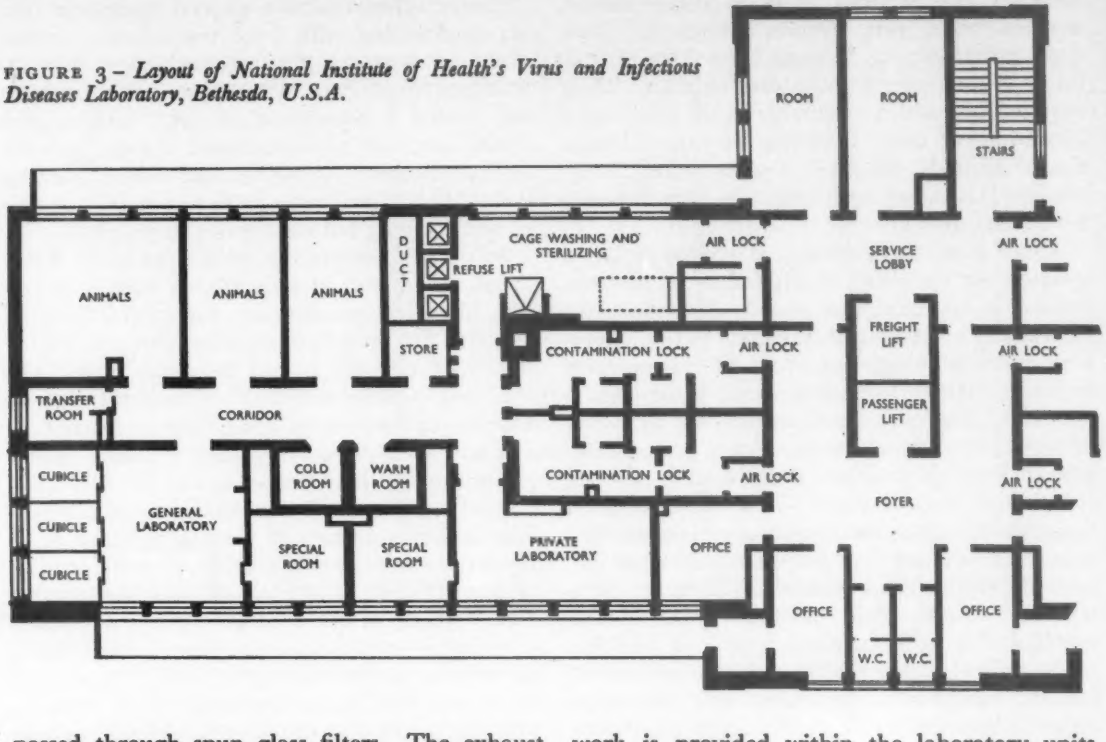


FIGURE 2 – *Preliminary layout of Merck isolation building, New Jersey.*

FIGURE 3 – *Layout of National Institute of Health's Virus and Infectious Diseases Laboratory, Bethesda, U.S.A.*



passed through spun glass filters. The exhaust air from these areas and hoods is sterilized by passing it through electric grills. Figure 3 shows the layout of one of the two identical laboratory wings on each floor. The essential features are dressing rooms and decontamination locks, small and large laboratories with special rooms and sterile cubicles, constant-temperature rooms, animal rooms, and cage washing and sterilizing room.

In these units rather less than half the floor area is available for laboratory space; about a third is taken up by animal quarters and sterilizing area, and the remainder is taken by the contamination locks and circulation. All writing work, the reading of literature, and other non-experimental activities of the workers, are conducted in offices and rooms of the central clean areas. No desk space for non-experimental work is provided within the laboratory units.

Merck, at Rahway, New Jersey, have suggested another approach to the prevention of infection, the general principle of which is shown in the preliminary layout of their isolation building (see figure 2). The building is single-storied and will ultimately be in the form of a cross, with the root accommodating the incineration, washing, and sterilizing facilities. Each wing is divided along its length by a solid wall into two completely self-contained infected areas. Here again a considerable proportion of the floor space is taken up by the essential decontamination locks, sterilizing, washing, and incineration facilities.

The author gratefully acknowledges his indebtedness to American colleagues and Institutions for placing many of the essential data at his disposal, and for their generous assistance and co-operation.

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Blood-pigments

H. MUNRO FOX

In vertebrate animals haemoglobin is the respiratory blood-pigment which transports oxygen from lungs or gills to muscles and other tissues. Among the invertebrates, some have haemoglobin but others have a related green pigment, chlorocruorin, or the blue haemocyanin, while yet others have no blood-pigment at all. Substances nearly related to haemoglobin and chlorocruorin are found in tissue cells of all animals. The functions, relationships, origin, and evolution of the respiratory pigments are discussed in this article.

Blood is coloured because it contains a respiratory protein. This means a chemical substance which can attach dissolved oxygen to itself and then give it up again when the pressure of oxygen in the surroundings is low. Haemoglobin is such a substance. It enables our blood to carry forty times the amount of oxygen from lungs to muscles, brain, and glands that water could transport in solution. As we need this oxygen, we could not exist without haemoglobin, for clearly it would be impossible to have forty times our normal volume of blood. All vertebrate animals possess haemoglobin. Many invertebrates also have blood which is red with haemoglobin. Some, however, have a similar green pigment, others have blue blood, while yet others have no pigment at all in their blood. The octopus and the snail have blue blood. So have lobsters and crabs. This colour is due to haemocyanin [1], which is another respiratory protein, with copper in its molecule and not iron as in haemoglobin. Figure 7 (*a*) shows blue oxyhaemocyanin; deoxygenated it is colourless. Figure 7 (*c*) shows scarlet oxyhaemoglobin and figure 7 (*b*) the purple deoxygenated pigment.

Haemoglobin has a greater affinity for carbon monoxide than for oxygen. For this reason carbon monoxide is a poison, though some animals are not quickly killed by it. For example, the so-called blood-worm, the red larva of a midge, *Chironomus*, which lives in its millions in mud on the bottom of lakes, has haemoglobin in its blood. As long as the lake water is well aerated, the insect's haemoglobin is not used. The oxygen in simple solution in the insect's blood is then enough for its wants, and so one cannot at once kill the larva with carbon monoxide. However, in the mud where the insect lives oxygen is often scarce, and it is then that the haemoglobin comes into action (R. F. Ewer). It picks up the little oxygen available in the muddy water. The insect can indeed live for quite a long time with no oxygen at all, but such anaerobic life is costly, using up much stored food, and the insect keeps quite still when in the anaerobic state, not even feeding. Haemoglobin enables it to use the last traces of oxygen in the pond, staving off the anaerobic state (Walshe [2]).

Another invertebrate animal with haemoglobin in its blood is *Daphnia* [3]. This is a small crustacean abundant in many ponds, which Schwammerdam, in the seventeenth century, called the Arborescent Water-flea (figure 2). The haemoglobin in the blood of *Daphnia* has apparently no respiratory function. By means of carbon monoxide one can render the pigment incapable of carrying oxygen. With its haemoglobin thus inactivated, the animal goes on swimming for hours as vigorously as before, no matter how low the dissolved oxygen content of the water may fall. But *Daphnia* has an unexpected use for its blood-pigment. Female *Daphnia* carry their eggs in a brood-pouch (figure 4). Here the eggs develop in a couple of days into young, which then swim away. In the brood-pouch the eggs risk partial suffocation, since there is no free communication with the outside water. The eggs of *Daphnia* differ from all others in that they contain haemoglobin: see figure 4. Experiments have shown that the eggs develop less rapidly when their haemoglobin is put out of action by carbon monoxide. Thus the haemoglobin in the eggs does possess a function. Now, most surprisingly, during the few hours before the eggs are laid in the brood-pouch, while they are still in the mother's ovary, they become visibly pinker, while at the same time the blood of the mother becomes measurably paler (E. I. B. Dresel). The blood of the *Daphnia* supplies the eggs with haemoglobin. Here is an unexpected function for the blood-pigment.

In the study of haemoglobin, *Daphnia* is also remarkably interesting for a different reason. This is that the quantity of haemoglobin present in its blood varies very greatly. *Daphnia* in one

pond may all be pale; the same species in another pond can be so red that the whole water seems coloured. As Schwammerdam wrote, 'the water appeared as if changed into blood, which, indeed, terrified me at first.' One and the same individual *Daphnia* can change in the course of a few days from being almost colourless to red, and *vice versa*. The contrast is well seen in figures 2 and 3. The cause of an increase in haemoglobin in the blood of *Daphnia* is a low oxygen content of the water in which the animal lives. It was once thought that the increase in blood-pigment of *Daphnia* was due to their eating green algae. This was explained by the chemical similarity between chlorophyll and haem, the coloured part of the haemoglobin molecule, for both chlorophyll and haem are built up from porphyrins, cyclic compounds with four pyrrol rings. In fact, however, chlorophyll in the food does not produce haemoglobin in *Daphnia* (S. M. Hardcastle), any more than patent medicines based on chlorophyll cure human anaemia. In point of fact, *Daphnia* in a polluted farm pond lacking oxygen behave like human mountain climbers, for extra haemoglobin appears in a mountaineer's blood in response to an oxygen deficit in the air.

In mammals, red blood-cells with haemoglobin are formed in the marrow of bones. This is an unexpectedly out-of-the-way place for such an important synthesis. Could the cause of it be that there is perhaps in the bone marrow a backwater of the blood-stream in which oxygen is deficient? The events in *Daphnia* and in mountaineers suggest that haemoglobin may be a by-product of semi-anaerobic metabolism. Once, in early geological times, some hundreds of millions of years ago, haemoglobin must have been synthesized in an animal for the first time. To begin with, it may well have been merely a useless by-product of semi-anaerobic life. Later on, the usefulness, in some cases, of haemoglobin as an oxygen carrier or an oxygen store would have assured its preservation through natural selection. In other cases it may still occur as a useless by-product, in yet others as a vestigial remnant of a substance formerly useful.

The distribution of haemoglobin in the animal kingdom is rather worrying to zoologists, who like to find everything fitting into a clear genealogical plan, as anatomical structures usually do. All vertebrate animals have haemoglobin; it is common in the *Annelida* (as the earthworm) and the *Entomostraca* (which include *Daphnia*). But why do only one or two of the hundreds of thousands of insect species possess it, as does *Chironomus*, and why only one or two of all the molluscs, as for example the pond snail *Planorbis*? One reason must be that haem, the coloured part of the haemoglobin molecule, is present in most animal cells, whether or not there is haemoglobin in the blood (Keilin [4]). Haem is usually present in cells in very small amounts—so small that it cannot be detected by its colour or be extracted. With pyridine, however, haem forms a compound known as a haemochromogen, with a characteristic strong absorption band easily detected by a spectroscope. In those animals in which the most widely distributed variety of haem, namely protohaem, happens to meet the right protein, globin, haemoglobin may be formed. Haemoglobin occurs in plants too: it is found in the root nodules of beans and peas.

This does not end the spasmodic distribution of respiratory blood-pigments in the animal series. A very few animals have blood which is green. This colour is due to a respiratory protein which Ray Lankester in 1867 called chlorocruorin [5]. The only animals which possess chlorocruorin are certain annelid worms (*Serpulimorpha*) living in the sea. Figures 1 and 5 show photographs of the living animals. The body of the worm is concealed in a protective tube. From one end of the tube projects a beautiful crown of tentacles which serve for respiration and for collecting food. When a small individual is removed from its tube and the blood-vessels are observed through the translucent body with a microscope, the strange appearance is seen of light green blood in the smallest blood-vessels but deep red blood in the larger vessels. Both colours are due to chlorocruorin, for it is a dichroic substance. It appears red when seen in thick layers or in concentrated solution, but green in a thin layer or when dilute. This is shown in figure 7(*d*), which is a colour photograph of the blood of *Sabella*, diluted with water, in a wedge-shaped trough. At one end the chlorocruorin is red, at the other green. Dichroism has a simple explanation, revealed by the spectroscope (see figure 6). When the light passes through a thick layer of a chlorocruorin solution most of it is stopped and only red rays pass (figure 6 (*a*)). With a lesser thickness more light passes, some of which is green and blue (figure 6 (*b*)), the resultant colour appearing green.

Chlorocruorin is chemically nearly related to haemoglobin, although so different in colour. Both are proteins united to haem, which contains iron. Separation of haem from the protein and

FIGURE
chlorocru
breathing

IGURE
lood.

FIGURE 1 – Sabella Spallanzanii, *a marine animal with green chlorocruorin in its blood. On the left the orange food-catching and breathing organ is emerging from the tube.*

FIGURE 2 – Daphnia magna, *an inhabitant of ponds, with haemoglobin in its blood.* (×10)

FIGURE 3 – Daphnia magna *with very little haemoglobin in its blood.*

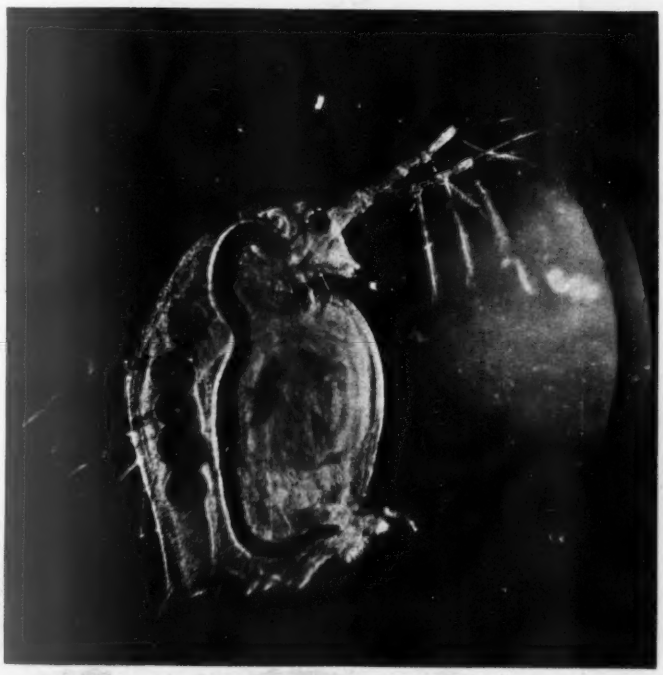

FIGURE 4 – Daphnia magna *carrying in its brood-pouch four eggs with haemoglobin in them.*

Sabella *and* Daphnia (*figures* 1–5) *were photographed alive.*

FIGURE 5 – Sabella pavonina, *another marine animal with green chlorocruorin in its blood.*

[*From C. M. Yonge's* The Sea Shore (*Collins*), *by courtesy of the author, publishers, and Adprint Limited.*]

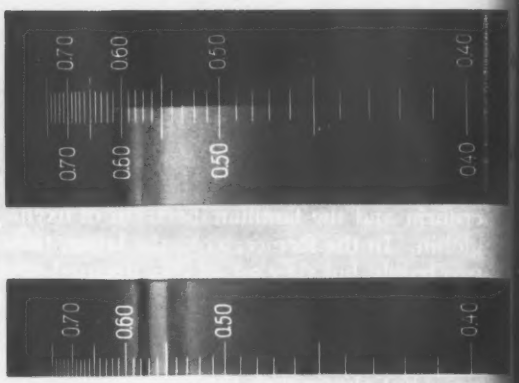

FIGURE 6 – *Absorption spectra:* (a) *concentrated solutio of oxychlorocruorin,* (b) *dilute oxychlorocruorin,* (c) *oxy haemoglobin. Each division of the wavelength scale* 100 A.

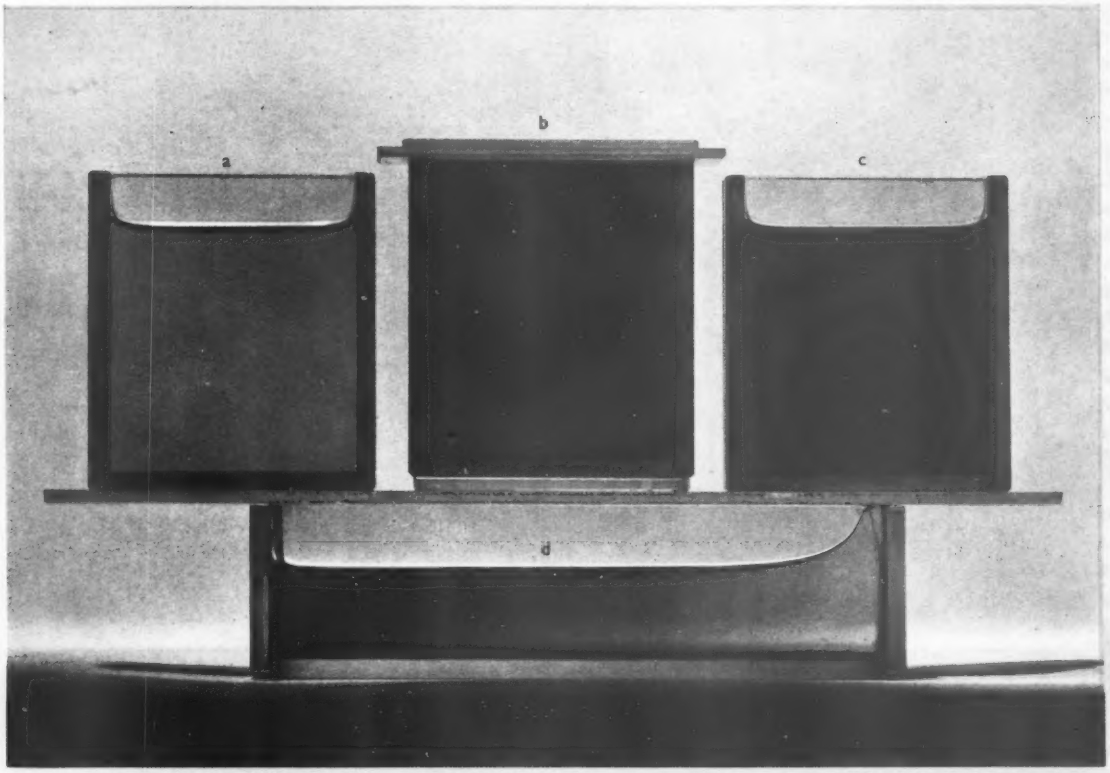

FIGURE 7 – *Bloods of different colours.* (a) *Octopus blood containing oxyhaemocyanin,* (b) *diluted human blood with the haemoglobin deoxygenated,* (c) *diluted human blood with oxyhaemoglobin,* (d) *diluted blood of* Sabella *in a wedge-shaped trough, narrow on the right, showing the dichroism of chlorocruorin.*

d solution
(c) oxy-
scale is

removal of its iron atom leaves a porphyrin. The porphyrin of chlorocruorin differs from that of haemoglobin only in one side-chain of one of its four pyrrol rings: here there is an aldehyde instead of a vinyl group (Hans Fischer). Figure 6 shows the absorption spectrum of oxychlorocruorin and the familiar spectrum of oxyhaemoglobin. In the former, as in the latter, there are two bands, but they are of very unequal intensity and are displaced towards the red. Each derivative of chlorocruorin has its characteristic absorption spectrum, corresponding to the haemoglobin series but always with the bands farther from the blue. These spectra have enabled chlorocruorin to be studied in the very small quantities in which it is obtainable. Chlorocruorin is the respiratory blood-pigment of nearly all the serpulimorph annelid worms, with two strange exceptions [6]. *Spirorbis* forms tiny coiled white calcareous tubes on seaweeds and rocks. The blood of one species in this genus contains chlorocruorin, but another species has haemoglobin in its blood in place of chlorocruorin, and yet another lacks either pigment. Nor is this the whole of the bizarre distribution of respiratory proteins among these animals, for *Serpula* possesses both chlorocruorin and haemoglobin together in its blood. There is no other animal known to have two respiratory blood-pigments. No functional reason has been suggested for this duplication.

Chlorocruorin might appear to be a mere biochemical curiosity, a small sideline in evolution, striking perhaps owing to its colour but otherwise unimportant, as it occurs only in a very few marine animals. Yet this is not the case. A substance akin to chlorocruorin is present, not in the blood but in many of the body cells—muscle cells, spermatozoa, etc.—of the majority of animals, including man. Living cells not only have protohaem in them; many contain several haem compounds known collectively as cytochrome (Keilin [4]). The reversible oxidation and reduction of cytochrome is an essential step in the oxidation of carbohydrates, etc., which supplies energy for muscular contraction and other life activities. Cytochrome is composed of three haem compounds, each with a different variety of haem and each with characteristic absorption bands. One of the three components of cytochrome contains the protohaem of haemoglobin. Another has a haem which, although not identical spectroscopically with that of chlorocruorin, is very near to it. The comparison of chlorocruorin derivatives with this cytochrome component has greatly aided its study. Here is a good example of a research, that on chlorocruorin, apparently narrow and academic, which turns out to have wide implications, both in comparative physiology and in medicine, for cytochrome is present not only in man but in bacteria causing human disease.

Haemoglobin, chlorocruorin, and haemocyanin are not the only respiratory blood-pigments. A fourth is known: it is a pink iron-containing protein called haemerythrin, found in a few marine invertebrates (e.g. *Sipunculus* and *Lingula*). There are no colourless oxygen-carrying proteins. I have given the names of the respiratory pigments in the singular, but the plural should really be used, for there are as many varieties of each pigment as there are species of animals possessing them. Specific haemoglobins differ from one another in the exact wavelength of the axes of their absorption bands [7]. Not only do specific haemoglobins exist, but more than one kind of haemoglobin may be found in one and the same animal, for haemoglobin occurs in tissue cells as well as in blood. Meat is red, not only because of red blood corpuscles in its capillary blood-vessels but owing to haemoglobin in the muscle cells themselves. In any one species of vertebrate animal the haemoglobins of blood and of muscle are spectroscopically different from one another. Are there also individual differences? The structural and functional diversity of individual animals and men must in the end be due to individual proteins. Since haemoglobin is a protein, one may ask whether individual haemoglobins can be detected. The answer is yes [8]. Individual rabbits can be distinguished by slight differences in the wavelength of the axis of an oxyhaemoglobin absorption band. The next step was to test human beings, but here the result was disappointing. Although the most diverse types of humanity of both sexes were tested—English, African, Chinese, Jewish—no measurable differences between their haemoglobins could be found.

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Book reviews

THE HUMAN SIDE OF CHEMISTRY

Humour and Humanism in Chemistry, *by John Read. Pp.* 368, *with* 90 *half-tone illustrations. G. Bell and Sons Limited, London.* 1947. 21*s. net.*

The Alchemist in Life, Literature, and Art, *by John Read. Pp.* 90, *with* 29 *half-tone illustrations. Thomas Nelson and Sons Limited, Edinburgh.* 1947. 10*s* 6*d. net.*

Professor Read is to be congratulated upon two excellent books which portray chemists, past and present, as human beings rather than as impersonal automata engaged merely in the collection of facts and the formulation of theories. Both are written, as one has come to expect, in excellent style and with a delicate sense of humour. These books are not only enjoyable reading but, at a time when the dangers of over-specialization are beginning to receive serious attention by educationists, are valuable for cultivating the liberal outlook which seems to have been so important a factor in the greatest scientific advances of the past. It is greatly to be hoped that Professor Read will find time to write more books of the same kind, for he can thus render a most valuable service to the advancement of science.

The Alchemist in Life, Literature, and Art is an analysis of the private lives of alchemists, the information being drawn from such varied sources as Chaucer's *Canon's Yeoman's Tale* and Jonson's play *The Alchemist*, engravings from works on alchemy, and paintings (especially those of David Teniers the younger). The whole is prefaced by a clear account of the principles which guided the alchemists in their work. The publishers as well as the author are to be congratulated, for despite austerity regulations the book is finely produced and well illustrated.

Humour and Humanism in Chemistry deals with a remarkable variety of people and an equally remarkable variety of events. Here we find described such diverse incidents as James IV's philological experiment in the Firth of Forth, Pepys's visit to 'the King's little elaboratory,' and F. J. Stoakley's unhappy experience with the cat and the aspidistra. Particularly interesting are the later sections in which Professor Read writes of the many chemists with whom he has had personal contact, and of his own experiences as a *Doktorand* at Zürich. This is a book which every chemist should read.

CONSERVATION OF PICTURES

The Care of Pictures, *by George L. Stout. Pp. viii* + 125. *Columbia University Press, New York.* 1948. $3.75 *net.*

The conservation of works of art by every available scientific means is a subject of great contemporary interest, but much of this work involves special apparatus unlikely to be available except in large institutions. Mr Stout has now written a book of modest size in which the whole matter is discussed with quite exceptional clarity and charm. Broadly, his aim has been to explain how pictures may be cared for, taking them as structures of a complex physico-chemical nature. Each step in the appropriate treatment is explained with the help of detailed diagrams specially prepared by the author. The use of complicated technical machinery is not assumed, though its role is mentioned fully in an appendix. A number of actual examples are described in order to bring out the specific action of solvents and their powers and limitations. The three-dimensional nature of the problem is kept always in view; restoration and repair (as well as preventive measures) involve operations in depth as well as on the surface. It is clear that many of these processes can be handled only by an expert, which indicates the need for a thorough scientific training at the highest professional level if the task of conservation is to be adequately undertaken. None the less, Mr Stout's book is delightfully readable; it forms the practical basis of the inquiry described in an article in *Endeavour* for July 1948. IAN RAWLINS

HIGH POLYMERS

The Chemistry of High Polymers, *by C. E. H. Bawn. Pp.* 249. *Butterworth's Scientific Publications, London.* 1948. 17*s.* 6*d. net.*

This book is based on a series of post-graduate lectures given in Bristol University in 1946 and is the first publication in this country covering the general principles of common applicability to macromolecules. Before the appearance of this book the student had to depend on the many excellent but highly specialized treatises and review articles which have been published both in America and in Europe during the last ten years. The attempt to cover the many aspects of high polymers in a book of just over 200 pages must inevitably lead to the subject-matter being somewhat condensed, and this applies more especially to the chapters dealing with the kinetics of polymerization and with the solid state, and those readers with no previous knowledge of the subject-matter may therefore find the book rather formidable. However, the student will find no part of the subject neglected, and is guided in his further reading by the extensive and well-selected references given at the ends of the chapters. A most welcome feature of this book is the provision of excellent diagrams, particularly those of molecular structures. J. C. SWALLOW

CURARE

Curare, its History, Nature, and Clinical Use, *by A. R. McIntyre. Pp.* 240, *with several half-tone and line illustrations. The University of Chicago Press, Chicago.* 1947. 27*s.* 6*d. net.*

This book is of a type which an increasing tendency towards specialization is making all too rare. Not only does Professor McIntyre give a detailed account of the chemistry and pharmacology of curare and of its clinical use—fields in which his own work is well known—but he gives also an excellent history of the drug from its earliest description by Peter Martyr. A botanical section gives a full account of all that is known of the ingredients of the various kinds of native curare. The text is accompanied by an exhaustive bibliography, a full index, and a number of good illustrations. The author's own views of curarization and of the possible uses of curare in medicine are of particular interest. The book is timely because of the growing recognition of the therapeutic possibilities of curare; those professionally engaged in this field of research will find it indispensable as a work of reference.

Apart from its intrinsic scientific value curare is a remarkable substance in its history, its method of preparation, and its properties. This scholarly and well-composed account of the poison should prove of interest to all scientists, whether or not they have a direct professional interest in curare.

Notes on contributors

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Was born in Budapest in 1891. He became a Member of the *Kaiser Wilhelm Institut für Physikalische Chemie* in 1923 but resigned in 1933 as a protest against anti-Jewish legislation. He was then appointed Professor of Physical Chemistry at Victoria University, Manchester. He was awarded honorary degrees (D.Sc.) by Princeton University in 1946 and by Leeds University in 1947. In 1948 he resigned the Chair of Physical Chemistry at Manchester University to take up an appointment as Professor of Social Studies in the same university. His publications include a theory of van der Waals adsorption (1916); X-ray analysis of fibres by the rotating crystal method (1921); plasticity of single crystals (1921–3); and study of reaction mechanism (1923–48). He is a founder member of the Society for Freedom in Science and has written many papers on the problems of science and society.

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Was born in 1884 and was educated at Manchester Grammar School and Manchester University. After doing research under the late Professor W. H. Perkin, he was appointed to the staff of the University of Manchester in 1907. In 1910 he became Professor of Chemistry at the Presidency College, Madras. During the war of 1914-18 he was Chemical Adviser to the Indian Munitions Board, and subsequently held the post of Forest Chemist at the Forest Research Institute and College, Dehra Dun. Later he was Professor of Organic Chemistry, Indian Institute of Science, Bangalore. In 1930 he succeeded Professor K. J. P. Orton in the Chair of Chemistry, University College of North Wales, Bangor, and held this appointment until 1943, when he was appointed Director of Research to the Colonial Products Research Council. He was president of the Indian Science Congress in 1928 and president of Section B, British Association, in 1947.

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Was born in 1902 in Essex and was educated at the King James School, Almondbury, Yorks. He became a student of the Institute of Mechanical Engineers and subsequently received his degrees from the University of Chicago, where he was later appointed to the faculty. Returning to Europe, he travelled and continued his studies on the Continent and in Britain. In 1931 he was invited to join the faculty of the University of Michigan Medical College, where he continued his investigation of the posterior pituitary gland. In 1932 he joined the faculty of the University of Nebraska Medical College and was appointed to the Chair of Physiology and Pharmacology in Omaha. Professor McIntyre and his collaborators have extensively investigated the effects of drugs and metallic ions on nerve and muscle mechanisms.

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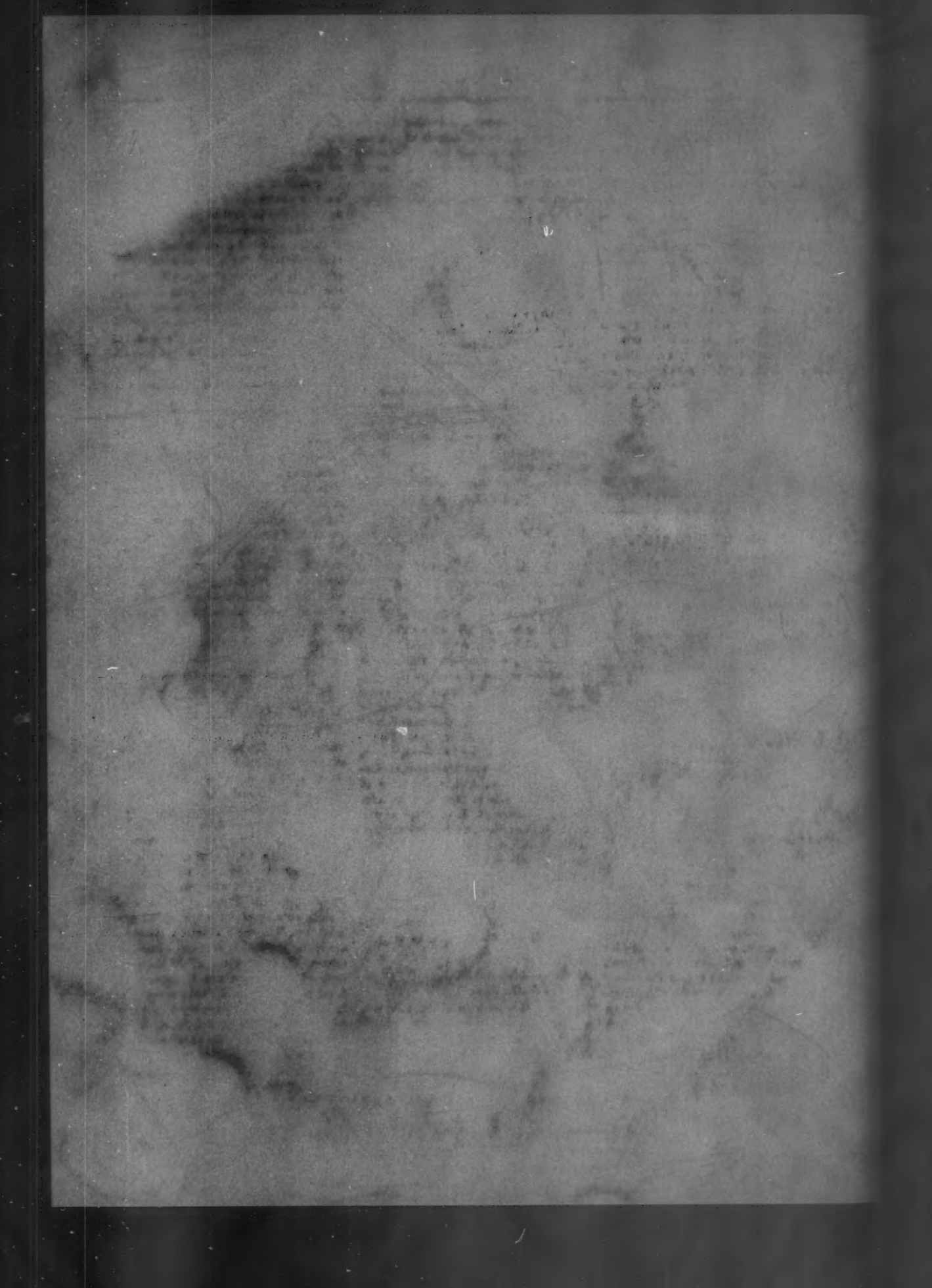
Was born in London in 1889 and was educated at Brighton College. He obtained a senior entrance scholarship to Gonville and Caius College, Cambridge, in zoology and geology, subjects not taught at his school. After serving in the first world war he spent some years in Egypt, where he investigated lunar periodicity in the reproduction of marine animals and migrations through the Suez Canal. Then, as a Fellow of Caius, he started his work on blood-pigments. His main research interests are in the physiology of aquatic invertebrates. Now Professor of Zoology at Bedford College in the University of London, he previously held the Chair in Birmingham. For twenty-four years he has edited *Biological Reviews.* He is vice-president of the International Union of Biological Sciences.

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